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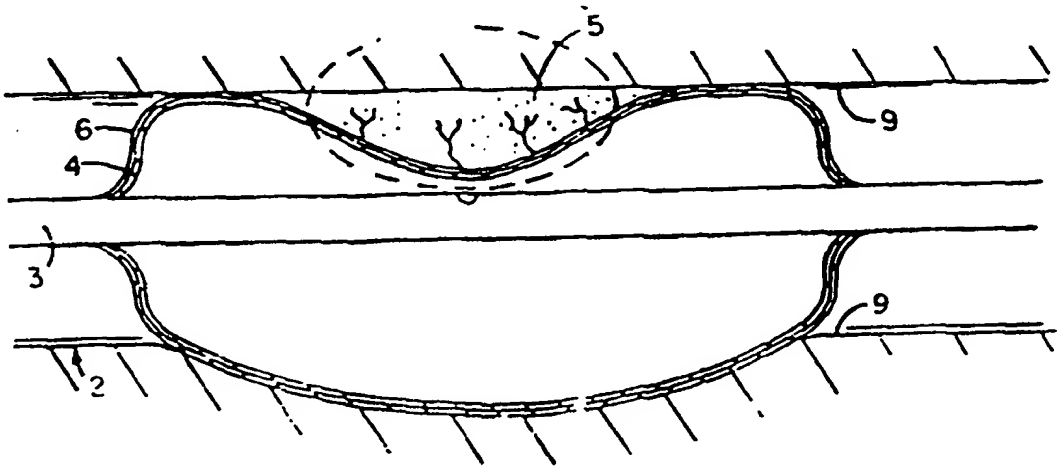

(57) Abstract

A medical device, polymer composition, and method for delivering substantially water–insoluble drugs to tissue at desired locations within the body. At least a portion of the exterior surface of the medical device is provided with a polymer coating. Incorporated in the polymer coatings is a solution of at least one substantially water–insoluble drug in a volatile organic solvent. The medical device is positioned to a desired target location within the body, whereupon the drug diffuses out of the polymer coating.

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LOADING AND RELEASE OF WATER-INSOLUBLE DRUGS

FIELD OF THE INVENTION

The invention relates to methods and devices for the localized delivery of substantially water-insoluble drug agents within the body.

BACKGROUND

The systemic administration of drug agents, such as by transoral or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because, for example, the drug agents may have unwanted effects on parts of the body which are not to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration.

It is therefore often desirable to administer drug agents at a localized site within the body. Common examples include cases of localized disease or occluded body lumens. Various methods have been proposed for such localized drug administration. For example, U.S. Patent No. 5,304,121, hereby incorporated by reference, discloses a method of delivering water-soluble drugs to tissue at desired locations of a body lumen wall. The method generally includes the steps of impregnating a hydrogel polymer on an expandable catheter with an aqueous drug solution, inserting the catheter into a blood vessel to a desired location, and expanding the catheter against the surrounding tissue allowing the release of the drug to the tissue. This method of localized drug delivery using hydrogel polymer impregnation has a limitation of being applicable to drug agents which are dissolved in water at concentrations

sufficient for therapeutic gel loading levels. There thus exists a need for a method and apparatus for the localized delivery of drug agents within the body, where the drug agents are substantially water-insoluble.

SUMMARY OF THE INVENTION

One objective of the present invention is to provide a method and apparatus for the localized delivery of substantially water-insoluble drug agents to predetermined locations within the human body.

A further objective of the present invention is to provide a method and apparatus to facilitate gradual, localized release of drug agents at predetermined locations within the human body.

A further objective of the invention is to administer drug agents by diffusion directly into the tissue requiring treatment. The drug is preferably applied in a manner that does not further injure the tissue to be treated, and administration is selectively and evenly distributed over the treated area such that the drug can be taken up by the tissue, without, for example, being washed away by body fluids.

The present invention provides methods and medical devices for the localized delivery of substantially water-insoluble drugs agents.

A particular embodiment of the present invention features a catheter and method for delivering substantially water-insoluble drug agents to tissue at a desired location along body lumen walls. The catheter is constructed for insertion in a body lumen and has a catheter shaft and an expandable portion mounted on the catheter shaft. The expandable portion is expandable to fill the cross-section of the body lumen. At least a portion of the exterior surface of the expandable portion is defined by a polymer coating. Incorporated into the polymer coating is at least one substantially water-insoluble drug. The catheter is positioned to a desired

target location within the body, whereupon the polymer coating absorbs water, thus dissolving the drug and resulting in the diffusion of the drug out of the polymer coating. The polymer and drug are selected to allow controlled release of a desired dosage of the drug from the polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1a shows one embodiment of the present invention in which a drug solution is impregnated into a polymer-coated balloon catheter.

Fig. 1b shows the insertion of a polymer-coated balloon catheter into a body lumen, in accordance with the present invention.

Fig. 1c shows the expansion of a polymer-coated balloon catheter at an occlusion site within a body lumen, in accordance with the present invention.

Fig. 2 shows a drug delivery balloon catheter embodiment of the present invention including a sheath for covering the catheter as it is being moved through a vessel toward the occlusion to be treated.

Figs. 3a and 3b show the release profile of paclitaxel from a balloon catheter having a polyacrylic acid-based coating for up to 50 and 5000 minutes, respectively, in accordance with the present invention.

Figs. 4a and 4b show the release profile of dexamethasone from a balloon catheter having a polyacrylic acid-based coating for up to 30 and 400 minutes, respectively, in accordance with the present invention.

Fig. 5 shows the release profiles of molsidomine from various balloon catheters having a polyacrylic acid-based coating for up to 5 minutes, in accordance with the present invention.

Fig. 6 shows the release profiles of dexamethasone from various balloon catheters having a polyacrylic acid-based coating for up to 450 minutes, in

accordance with the present invention.

Figs. 7a and 7b show the release profiles of water-soluble and substantially water-insoluble estradiol from balloon catheters having a polyacrylic acid-based coatings for up to 10 and 200 minutes, respectively, in accordance with the present invention.

Fig. 8 shows the release profile of paclitaxel for up to 10 days from polyurethane coated stents dipped in 30 mg/ml paclitaxel in ethanol for 3 days, in accordance with the present invention.

Fig. 9 shows the release profiles of paclitaxel from various polyurethane-coated balloon catheters for up to 2 hours, in accordance with the present invention.

DETAILED DESCRIPTION

The present invention provides methods and medical devices for the localized delivery of one or more substantially water-insoluble drug agents to predetermined locations within the human body.

In accordance with an embodiment of the invention, a substantially water-insoluble drug agent is dissolved in a volatile organic solvent. "Organic solvent" is intended to mean a singular organic solvent or a solvent mixture having at least one organic component. The solvent mixture also includes mixtures of water with miscible organic solvents. The drug solution is then applied to a polymer coating on a medical device that is adapted for insertion into the body. Examples of such medical devices include catheters, guide wires, balloons, filters (*e.g.*, vena cava filters), stents, stent grafts, vascular grafts, implants and other devices used in connection with drug-loaded polymer coatings.

In a preferred embodiment, the polymer is provided in the form of a coating on an expandable portion of a catheter. After applying the drug solution to the polymer and evaporating the volatile solvent from the polymer, the catheter is inserted into a body lumen

where it is positioned to a target location. The expandable portion of the catheter is subsequently expanded to bring the drug-impregnated polymer coating into contact with the lumen wall. The drug is released from the polymer as it slowly dissolves into the aqueous bodily fluids and diffuses out of the polymer. This enables administration of the drug to be site-specific, limiting the exposure of the rest of the body to the drug.

The polymer used in the present invention is preferably capable of absorbing a substantial amount of drug solution. When applied as a coating on a medical device in accordance with the present invention, the dry polymer is typically on the order of about 1 to 10 microns thick, preferably about 2 to 5 microns. Very thin polymer coatings, *e.g.*, of about 0.2-0.3 microns and much thicker coatings, *e.g.*, more than 10 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto a medical device. Such multiple layers are of the same or different polymer materials.

The polymer of the present invention is hydrophilic or hydrophobic, and is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. The preferred polymer is polyacrylic acid, available as HYDROPLUS (Boston Scientific Corporation, Natick, Mass.), and described in U.S. Pat. No. 5,091,205, the disclosure of which is hereby incorporated herein by reference. U.S. Patent No. 5,091,205 describes medical devices coated with one or more polyisocyanates such that

the devices become instantly lubricious when exposed to body fluids.

By "substantially water-insoluble drug" is meant any therapeutic agent having a greater solubility in organics than in water. More specifically, such drugs have a water solubility of no greater than 1 part drug to 30 parts water, more typically no greater than 1 part drug to 1,000 parts water. Such solubilities are described as "sparingly soluble" to "very slightly soluble" in the art.

The drug agents used in the present invention are selected from a number of drug types depending on the desired application. For example, these drugs include anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, and analogues thereof; antineoplastic/ antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, thymidine kinase inhibitors, and analogues thereof; anesthetic agents such as lidocaine, bupivacaine, ropivacaine, and analogues thereof; anti-coagulants; and growth factors.

In accordance with the present invention, the drug agents are dissolved in a volatile organic solvent such as, for example, ethanol, isopropanol, chloroform, acetone, pentane, hexane, or methylene chloride, to produce a drug solution. The drug solution is then applied to the polymer. A volatile organic solvent typically is selected to provide drug solubilities much greater than the corresponding aqueous solubility for the substantially water-insoluble drug. Accordingly, application of the drug solution to the polymer often results in drug loadings that are orders of magnitude greater than loadings that can be achieved by application of a saturated aqueous solution of the drug to the polymer.

The drug solution is applied to the polymer coating by any suitable means, including dipping the polymer coating into the drug solution or by applying the solution onto the coating such as by pipet. In the former method, the amount of drug loading is controlled by regulating the time the polymer is immersed in the drug solution, the extent of polymer cross-linking, the concentration of the drug in the solution and/or the amount of polymer coating. In another embodiment of the invention, the drug is incorporated directly into the polymer prior to the application of the polymer topcoat as a coating onto a medical device.

After applying the drug solution to the polymer coating, the volatile solvent is evaporated from the coating, for example, by drying in air or in an oven.

The release profile of the drug from the polymer coating is determined by many factors including the drug solubility, and the thickness and porosity of the polymer coating. When an expandable member such as a balloon catheter is used to administer the drug, pressure can be used to increase the rate of drug transfer to the tissue. An increase in pressure increases the diameter of the balloon and therefore the diameter of the surrounding tissue, thereby increasing the surface area for drug transfer. The amount of drug that is delivered per unit time is therefore increased.

When an expandable catheter is chosen as the medical device of the present invention, the expandable portion is preferably a balloon, in which case the drug is placed in the polymer for controlled release of the drug upon expansion of the balloon against a body lumen. The expandable portion optionally includes a stent, mountable in a body lumen by expansion thereof. The catheter also optionally comprises a sheath member which is extendable over the expandable portion to inhibit release of the drug into body fluids during placement of the catheter.

Referring now to Figs. 1a-1c, an embodiment for the localized delivery of substantially water-insoluble drugs to a predetermined location within the body is described. The drug administration method shown in Figs. 1a-1c illustrates the use of the present invention in conjunction with an angioplasty process. Catheter device 1 comprises a body 3 having a balloon 4 attached at its distal end. The balloon 4 on the catheter 3 includes a polymer coating 6. As shown in Fig. 1a, drug solution 8 is impregnated into the polymer coating with the balloon in its substantially deflated state prior to insertion into the patient. As shown in Fig. 1b, after the volatile solvent is evaporated, the device 1 is inserted into a body lumen 2 having a region to be treated, such as an occlusion due to a deposition of plaque 5 on the lumen wall tissue 9. The device 1 is moved along the vessel to position the balloon 4 at the occlusion site, as shown in Fig. 1c. The lumen may be, for example, a narrow, tortuous opening through which the catheter is passed by torquing or other known techniques. As shown in Fig. 1c, the balloon is inflated to provide close contact between the drug-impregnated polymer coating 6 and the surrounding plaque and tissue. As water from the body penetrates into the polymer coating 6, it begins to dissolve the drug agent, which subsequently diffuses out of the polymer coating 6 and into the surrounding plaque and tissue.

During drug administration, a substantial amount of the drug contained in the polymer coating is diffused into the affected area. The inflation pressure needed to expand the balloon catheter and dilate the lumen, if necessary, is typically in the range of about 1 to 20 atm. The balloon is formed of any suitable materials such as vinyl polymers such as polyethylene; polyesters such as polyethylene terephthalate; polyamides such as nylon; polyolefins and copolymers thereof (*e.g.*, Selar, Pebax, Surlyn, Hytrel, etc.). The balloon is

optionally a perfusion balloon, which allows blood to perfuse the catheter to prevent ischemia during delivery. A perfusion balloon is particularly preferred for long arterial delivery times and when the delivery drug is only very slightly soluble in water.

Referring to the embodiment of the invention illustrated in Fig. 2, the balloon portion 4 of catheter 3 is optionally covered by a protective sheath 7 while the instrument 1 is inserted into a body lumen 2 and positioned at a treatment region. As the coated balloon 4 is positioned at occluded site 5, the protective sheath 7 is drawn back to expose the balloon 4. In an alternative embodiment, the sheath remains stationary while the catheter moves the coated balloon forward into the occluded region. The sheath 7 protects the coating and inhibits premature release of the drug. Such a sheath might be particularly advantageous when using drugs which are not sufficiently water-insoluble or if even minor delivery to tissue during catheter placement is a problem, *e.g.* for extremely toxic drugs.

Although Figs. 1 and 2 illustrate the application of the present invention to an angioplasty process, the present invention is also used to administer drug agents to target locations where there is no occlusive formation.

Procedures for preparing a drug delivery balloon catheter with a polymer coating are presented in the following non-limiting examples.

Example 1: Release kinetics of paclitaxel from polyacrylic acid-based coating.

A 2 mg/ml solution of paclitaxel is prepared in chloroform. The solution is gently agitated until the paclitaxel is completely dissolved. The solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating and inflated to 2 atm. A total of 100 μl of solution, and hence 200 μg of

paclitaxel, is applied to the catheter. The balloon catheter is then dried in air for 30 minutes and in a vacuum oven for 48 hours at 50°C to evaporate the chloroform. The catheter is then immersed in a solution of 1% dimethyl sulfoxide (DMSO) and phosphate buffered saline(PBS) having a pH of 7.4 for in-vitro drug release. The cumulative amount of paclitaxel released from the catheter coating yields the data shown in Figs. 3a and 3b.

Example 2: Release kinetics of dexamethasone from polyacrylic acid-based coating.

Solutions containing 1.5 mg/ml and 200 μg/ml of dexamethasone in chloroform, are prepared by gently agitating until the dexamethasone is completely dissolved. The solutions are separately applied via dripping to separate balloon catheters having polyacrylic acid-based coatings and inflated to 2 atm. A total of 100 μl of each solution is applied to each respective catheter, corresponding to dexamethasone loadings of 150 μg and 20 μg, respectively. These results can be contrasted with the inability to apply substantial amounts of dexamethasone to polyacrylic acid-based coatings using aqueous solutions, in which case only about 1 μg of dexamethasone can be loaded into such coatings. The balloon catheters are then dried in a vacuum oven for 2 hours at 50°C to evaporate the chloroform solvent. The catheters are thereafter immersed in PBS (pH = 7.4) to track the release of dexamethasone over time. The cumulative amount of dexamethasone released from each catheter yields the data shown in Figs. 4a and 4b.

Example 3: Release kinetics of molsidomine from polyacrylic acid-based coating.

Various solutions of molsidomine in volatile solvents are prepared and applied to balloon catheters by

the methods indicated in Table I. In the "dip" application technique, each balloon catheter having a polyacrylic acid-based coating is dipped into its respective solution for 10 minutes. In the "pipet" application technique, 200 μl of solution is pipetted onto its respective coated balloon catheter while slowly turning. All samples are dried in an oven for 30 minutes at 50°C and thereafter immersed in PBS (pH = 7.4) to track the release of molsidomine over time. The cumulative amount of molsidomine released from each catheter yields the data shown in Fig. 5a and 5b.

Table I. Molsidomine solution characterization, and methods of applying molsidomine solution to polymer coated catheters.

Sample	Solvent	Concentration (mg Molsidomine per ml solvent)	Application technique
1	chloroform	150	dip
2	chloroform	30	pipet
3	chloroform	150	pipet
4	ethanol	30	pipet
5	ethanol	30	dip

Example 4: Release kinetics of dexamethasone added to polyacrylic acid-based topcoat formulation.

Rather than forming a solution of dexamethasone in an organic solvent and then applying this solution to polymer-coated balloon catheters as in Example 2, dexamethasone is added directly to the polymer used to coat the balloon catheters. Dexamethasone is weighed out into 0.05 g, 0.1 g, and 0.2 g samples, each of which is each added to 1 ml lots of polymer topcoat solution containing polyacrylic acid, methyl ethyl ketone, dimethyl formamide, and t-butyl alcohol. The dexamethasone samples are mixed with the polymer topcoat

solutions until completely dissolved. The dexamethasone-containing polymer topcoat solutions are separately applied via dripping to separate, uncoated balloon catheters inflated to 2 atm. After drying in a vacuum oven for 2 hours at 50°C, the catheters are immersed in PBS (pH = 7.4) to track the release of dexamethasone over time. The cumulative amount of dexamethasone released from each catheter yields the data shown in Fig. 6.

Example 5: Comparative release kinetics for water-soluble and water-insoluble estradiol.

Estradiol is provided in both water-soluble and substantially water-insoluble forms. Water-soluble estradiol is applied to a balloon catheter coated with a polyacrylic acid-based coating by i) preparing a 10 mg/ml solution of water-soluble estradiol in deionized, ultra-filtered water; and ii) placing the balloon catheter, inflated to 2 atm, into 200 μl of the solution for 20 minutes. Water-insoluble estradiol is applied to a balloon catheter coated with a polyacrylic-acid based coating by i) preparing a 10 mg/ml solution of substantially water-insoluble estradiol in methanol; and ii) dripping 100 μl of the solution onto the balloon catheter. The catheters are thereafter immersed in PBS (pH = 7.4) to track the release of both water-soluble and water-insoluble estradiol over time. Greater release is observed for the substantially water-insoluble form of estradiol when compared to the water-soluble form. The cumulative amount of estradiol released from each catheter yields the data shown in Figs. 7a and 7b.

Example 6: In-vivo delivery of paclitaxel from polyacrylic acid-based coating.

A 9.8 mg/ml solution of radio-labeled paclitaxel in chloroform is prepared. A total of 50 μl of the solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating. The

paclitaxel from the coated balloon catheter is then released in-vivo to porcine arteries. After release for a predetermined amount of time, the paclitaxel remaining in the coating is extracted using two sequential ethanol washes. The amount of paclitaxel released in the pig bloodstream, as calculated from the amount of paclitaxel loaded into the coating minus that extracted from the coating after delivery, is shown in Table II.

Table II. Amount of paclitaxel released into pig bloodstream from an impregnated, polyacrylic acid-based coated balloon catheter, as a function of delivery time.

Amount of time in bloodstream	Amount of paclitaxel extracted from balloon after delivery (μg)	Amount of paclitaxel released in bloodstream (μg)	% of paclitaxel released in bloodstream
1 minute	182 ± 1	307	63
5 minutes	160 ± 30	330	68

Example 7: Delivery of paclitaxel to explanted porcine arteries from polyacrylic acid-based coating.

A 9.8 mg/ml solution of radio-labeled paclitaxel in chloroform is prepared. A total of 50 μl of the solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating. The coated balloon catheter is then delivered to an explanted porcine artery for 15 minutes. After delivery, the paclitaxel remaining in the coating is extracted using two sequential ethanol washes. The delivered paclitaxel is extracted from the vessel, also by using two sequential ethanol washes. In addition, the vessel is placed in tissue solvent and counted for paclitaxel. Using these extraction methods, at least 80% of the paclitaxel loaded onto the balloon catheter is recovered, as shown in Table III.

Table III. Paclitaxel recovery from ex vivo delivery to porcine artery.

Amount paclitaxel loaded onto balloon	489 μg
Amount paclitaxel extracted from the balloon after delivery	360 μg
Amount paclitaxel extracted from artery	30 μg
Amount paclitaxel counted from tissue solution	1 μg
Total paclitaxel measured	391 μg
Percentage of paclitaxel recovered	80%

Example 8: Release kinetics of paclitaxel from polyurethane-based stent coating.

Slotted tube stainless steel stents are coated with polyurethane by spraying a 1 wt% solution of CHRONOFLEX polyurethane (made by CT Biomaterials) in tetrahydrofuran directly onto the stent surface. The coated stents are dried in a vacuum oven for three hours at 70°C.

Each polyurethane coated stent is placed in a vial, which is filled to maximum volume (1.5 ml) with a solution of paclitaxel in ethanol, and sealed. The stent is stored in the vial for three days at room temperature. The stent is then removed from the vial and dried for one hour at 65°C.

The above procedure is conducted using solutions of varying concentrations. Each stent is analyzed for paclitaxel content by extraction in dichloromethane solvent. The results are presented in Table IV below. Samples 1 and 2 were obtained using a paclitaxel concentration of 10 mg/ml, samples 3 and 4 using a 20 mg/ml solution and sample 5 and 6 using a 30 mg/ml solution.

Table IV. Paclitaxel content.

Sample #	Paclitaxel conc. (mg/ml)	Paclitaxel content (μg)	Coating Wt. (μg)	μg Paclitaxel per μg coating
1	10	44.8	796	0.06
2	10	88.2	859	0.10
3	20	151.2	718	0.21
4	20	127.6	702	0.18
5	30	157.1	736	0.21
6	30	144.3	629	0.23

These results suggest that Paclitaxel loading is relatively independent of paclitaxel concentration above 20 mg/ml, assuming equilibrium is attained in the three-day period. Nevertheless, the 30 mg/ml paclitaxel concentration is chosen for release studies as it produces the maximum paclitaxel loading (21-23%), while still being sufficiently below the saturation concentration for paclitaxel in ethanol (39 mg/ml).

Seven polyurethane coated stents are loaded using a 30 mg/ml paclitaxel solution, removed and dried as set forth above. Paclitaxel from four of the stents is extracted in dichloromethane solvent. The results of this extraction are presented in Table V below:

Table V. Paclitaxel content.

Sample #	Paclitaxel conc. (mg/ml)	Paclitaxel content (μg)	Coating Wt. (μg)	μg Paclitaxel per μg coating
1	30	111.7	676	0.17
2	30	50	627	0.08
3	30	45.3	612	0.07
4	30	37.4	602	0.06

The remaining three stents are immersed in a

solution of phosphate buffered saline solution having pH 7.4 at 37°C. Cumulative release as a function of time is presented in Fig. 8.

Example 9: Release kinetics of paclitaxel from polyurethane-based balloon catheter coating.

Nylon balloons are coated with polyurethane by dipping into a 9 wt% solution of CHRONOFLEX polyurethane in dimethylacetamide. The balloons are dried in a vacuum oven overnight at 50°C.

Each polyurethane coated balloon is loaded with paclitaxel either by dipping the coated balloon into a paclitaxel and ethanol solution or by dripping a known volume of a paclitaxel and ethanol solution onto the balloon surface.

In the first instance, a stock saturated solution of paclitaxel in ethanol is prepared. Then the polyurethane-coated balloon is inflated and submerged in the paclitaxel stock solution in a tube. The tube and balloon are well-sealed to prevent solvent evaporation. After remaining in the tube overnight, the ethanol is evaporated from the balloon over a suitable time period, such as about fifteen minutes. Five "dip-coated" balloons are prepared in this fashion.

In the second instance, a stock solution of paclitaxel having a concentration of 10 mg/ml prepared. Twenty ml of this paclitaxel stock solution are then pipetted onto an inflated polyurethane-coated balloon, providing a total mass of 200 mg of paclitaxel per balloon. Afterwards, ethanol is evaporated from the balloon over a suitable time period, such as about fifteen minutes. Five "drip-coated" balloons are prepared in this fashion.

Two drip-loaded balloons and two dip-loaded balloons are taken and the paclitaxel extracted in dichloromethane to determine total paclitaxel content. The paclitaxel content of the dip-coated balloons is

found to be 1093 +/- 439 μg, while the drip-coated balloons are found to have 215 +/- 11 μg paclitaxel.

For comparison, nylon balloons are coated with paclitaxel/polyurethane by dipping the balloons into a dispersion of 14.5 wt% BAYHYDROL polyurethane (made by Bayer) and 2.6 wt% paclitaxel in a mixture of 73.6 vol% N-methylpyrrolidinone and 26.4 vol% water. Balloons are dried in a vacuum oven overnight at 50°C. The dried coatings contain 15% paclitaxel by weight. Nine balloons are formed. Seven balloons are tested for paclitaxel loading yielding an average of 196 +/- 44 μg paclitaxel after extraction in dichloromethane.

The remaining three drip-loaded balloons from above, the remaining three dip-loaded balloons from above, and the remaining two balloons with the 15% paclitaxel formulated coating are placed in a solution of phosphate buffered saline solution having pH 7.4 at 37°C, and cumulative paclitaxel release is measured as a function of time. The results of this study are presented in Fig. 9.

It is to be appreciated that the parameters described in the above examples are merely illustrative and that the present invention is not limited to such parameters. For example, in each of the examples provided, any suitable polymer may be used for the polymer coating, any suitable drying time periods and temperatures may be used, any suitable organic solvent may be used, any suitable method for applying the polymer coatings to the medical devices may be used, any suitable method for applying the drugs to the polymer coatings may be used, any suitable water-insoluble analogue of the disclosed drugs may be used, and any suitable drug loading concentrations may be used.

The present invention provides a previously unknown method and medical device for the localized delivery of substantially water-insoluble drugs. Those

with skill in the art may recognize various modifications to the embodiments of the invention described and illustrated herein. Such modifications are meant to be covered by the spirit and scope of the appended claims.

We claim:

1. A method comprising the steps of:

providing a polymer;

providing a medical device adapted for insertion in a body;

coating at least a portion of the exterior surface of the medical device with the polymer to form a polymer coating; and

applying a drug solution to the polymer, said drug solution comprising at least one substantially water-insoluble drug dissolved in an organic solvent.

2. The method of claim 1, further comprising the step of drying said polymer coating such that substantially all of said solvent is evaporated.

3. The method of claim 1, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

4. The method of claim 3, wherein said polymer is polyacrylic acid.

5. The method of claim 1, wherein said at least one substantially insoluble drug is selected from the

group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

6. The method of claim 1, wherein said organic solvent is selected from the group consisting of ethanol, isopropanol, chloroform, acetone, pentane, hexane, methylene chloride, and mixtures thereof.

7. The method of claim 6, wherein said organic solvent includes water.

8. The method of claim 1, wherein said step of applying a drug solution to said polymer includes the step of dipping said polymer into said drug solution.

9. The method of claim 1, wherein said drug solution is applied to said polymer before said polymer is coated onto said medical device.

10. The method of claim 1, wherein said drug solution is applied to said polymer after said polymer is coated onto said medical device.

11. The method of claim 1, wherein said medical device is selected from catheters, guide wires, balloons, filters, stents, vascular grafts, and implants.

12. The method of claim 11, wherein said medical device is a catheter comprising a shaft and an expandable portion mounted on said shaft, at least a portion of the exterior surface of the expandable portion being covered with said polymer coating.

13. The method of claim 1, further comprising positioning

said medical device at a desired location in a body lumen.

14. The method of claim 13, wherein said medical device is a catheter comprising a shaft and an expandable portion mounted on said shaft, at least a portion of the exterior surface of the expandable portion being covered with said polymer coating.

15. The method of claim 14, further comprising the step of expanding said expandable portion of said catheter.

16. The method of claim 15, wherein said catheter comprises a sheath member which is extendable over said expandable portion.

17. The method of claim 16, further comprising the steps of:

extending said sheath over said expandable portion prior to said positioning; and

exposing said expandable portion from said sheath prior to said expanding.

18. The method of claim 1, wherein said step of coating comprises the step of applying multiple layers of said polymer to said medical device.

19. A medical device for delivering a substantially water-insoluble drug at a desired location within a body, comprising:

a medical device adapted for insertion in a body; and

a polymer coating containing at least one substantially water-insoluble drug provided on at least a portion of said medical device, wherein said substantially water-insoluble drug has a water-solubility no greater than 1 part drug to 30 parts water.

20. The medical device of claim 19, wherein said drug has a water solubility no greater than 1 part drug to 1,000 parts water.

21. The medical device of claim 20, wherein said medical device is a catheter for delivering substantially water-insoluble drugs to a desired location within a body lumen, said catheter comprising:

a shaft;

an expandable portion mounted on said shaft; and

a polymer coating on at least a portion of said expandable portion of said catheter, said polymer coating being impregnated with at least one substantially water-insoluble drug.

22. The medical device of claim 21, wherein said expandable portion includes an inflatable balloon.

23. The medical device of claim 22, further comprising a sheath member extendable over said expandable portion.

24. The medical device of claim 19, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane

dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

25. The medical device of claim 24, wherein said polymer is polyacrylic acid.

26. The medical device of claim 19, wherein said at least one substantially water-insoluble drug is selected from the group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

27. The medical device of claim 21, wherein said expandable portion includes a stent.

28. The medical device of claim 19, wherein said polymer coating is layered.

29. A polymer containing at least one substantially water-insoluble drug.

30. The polymer of claim 29, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

31. The polymer of claim 30, wherein said polymer is polyacrylic acid.

32. The polymer of claim 29, wherein said at least one substantially water-insoluble drug is selected from the

group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

33. The method of claim 1, wherein said polymer is polyurethane.

34. The method of claim 1, wherein said medical device is a stent.

35. The method of claim 1, wherein said drug is paclitaxel.

36. The method of claim 1, wherein said medical device is a stent, said polymer is polyurethane, and said drug is paclitaxel.

37. The medical device of claim 19, wherein said polymer is polyurethane.

38. The medical device of claim 19, wherein said medical device is a stent.

39. The medical device of claim 19, wherein said drug is paclitaxel.

40. The medical device of claim 19, wherein said medical device is a stent, said polymer is polyurethane, and said drug is paclitaxel.

41. The polymer of claim 29, wherein said polymer is polyurethane.

42. The polymer of claim 29, wherein said drug is paclitaxel.

43. The polymer of claim 29, wherein said polymer is polyurethane and said drug is paclitaxel.

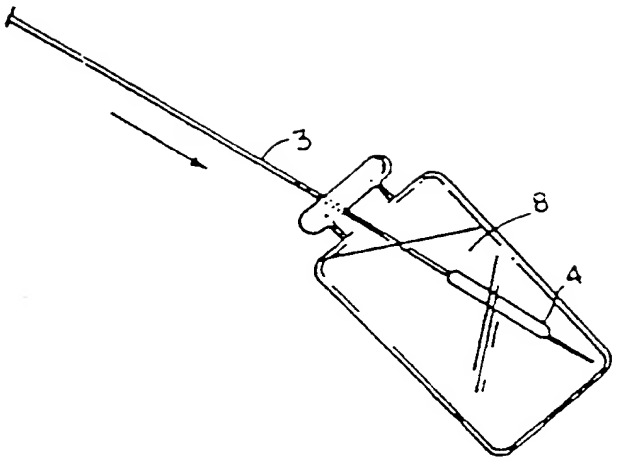

FIG. 1a

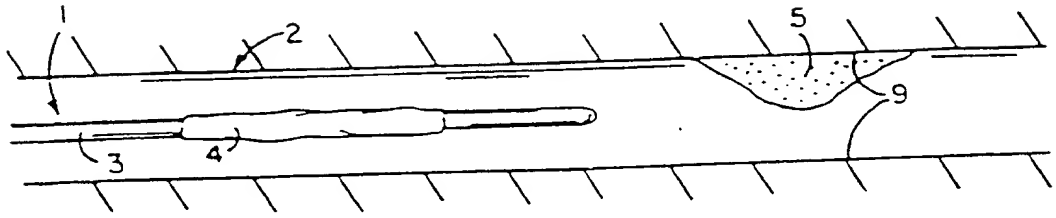

FIG. 1b

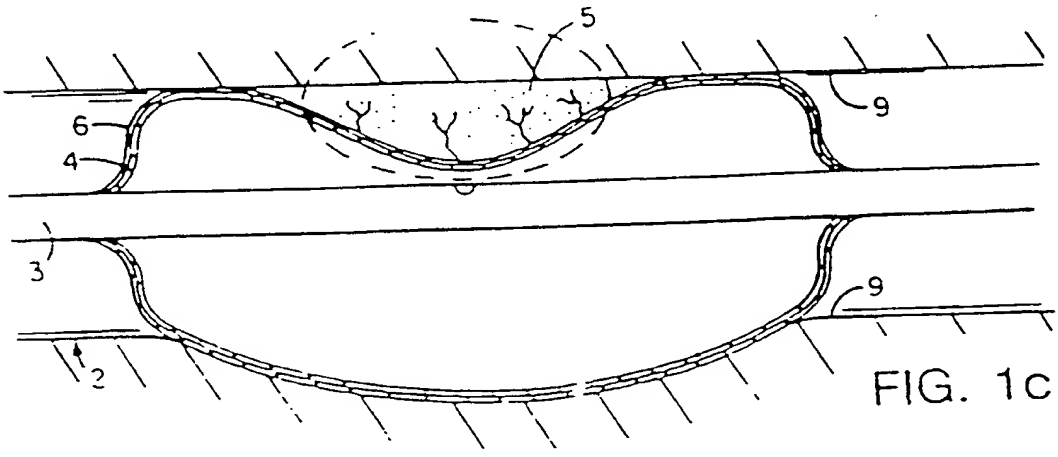

FIG. 1c

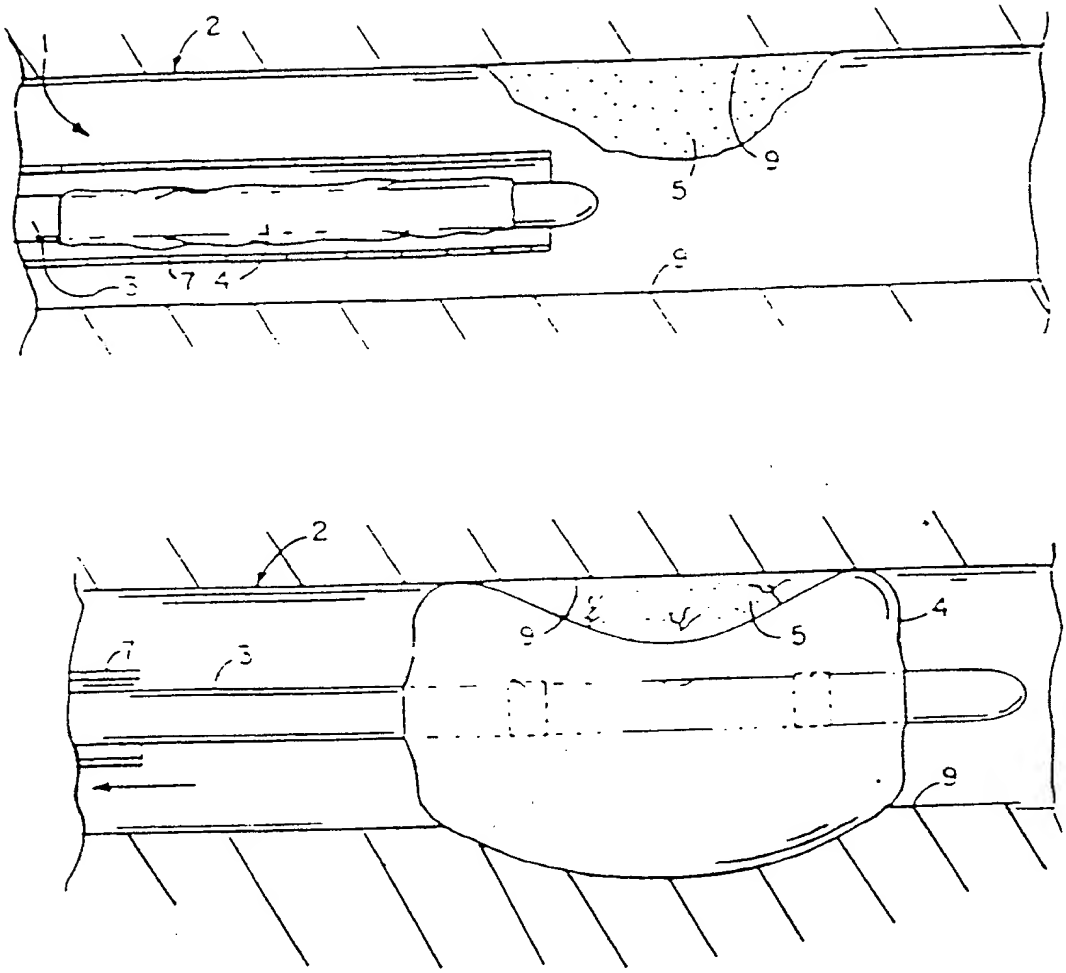

FIG. 2

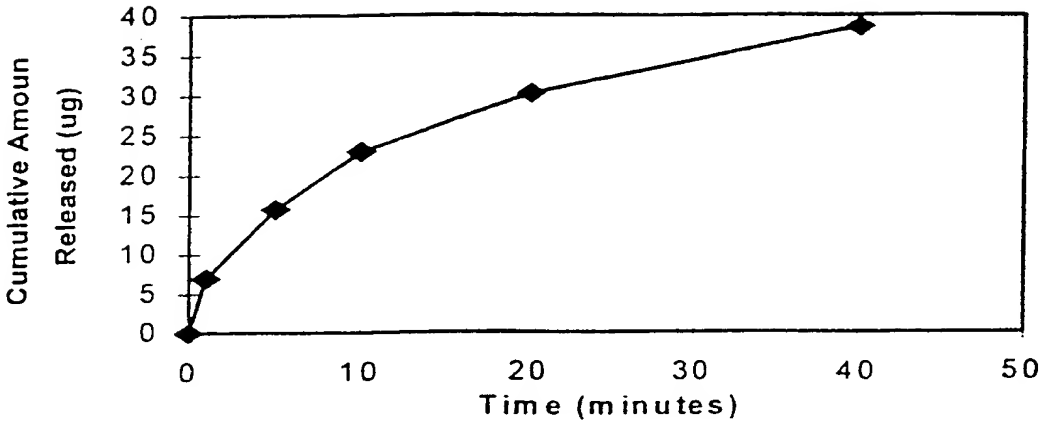

FIG. 3a

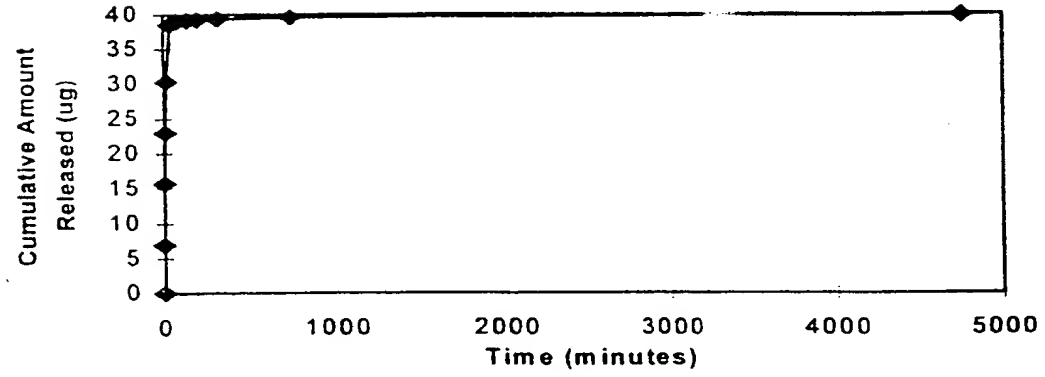

FIG. 3b

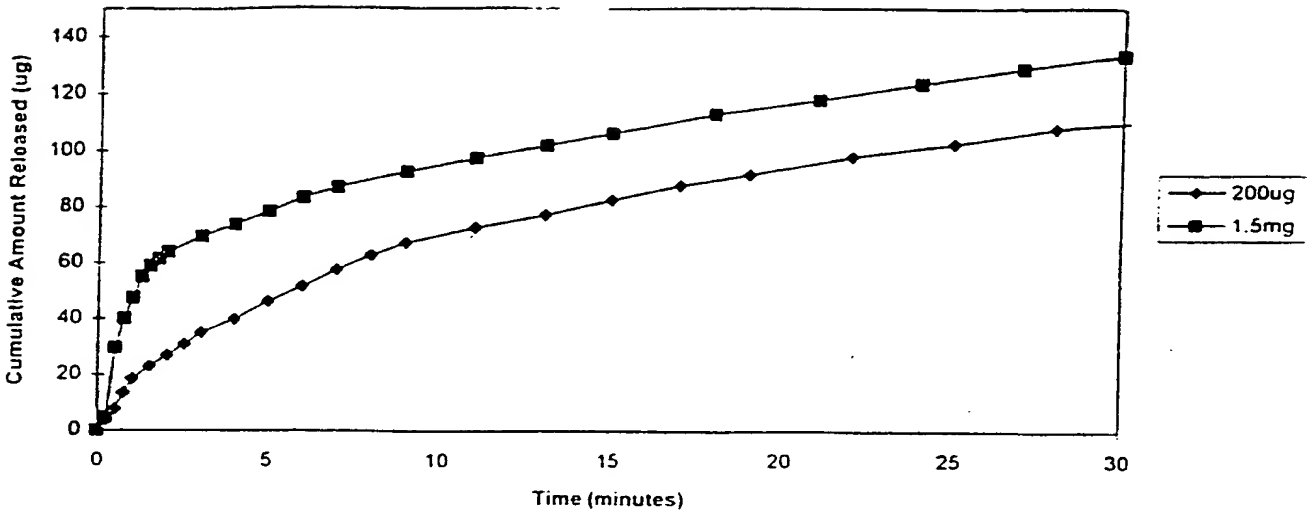

FIG. 4a

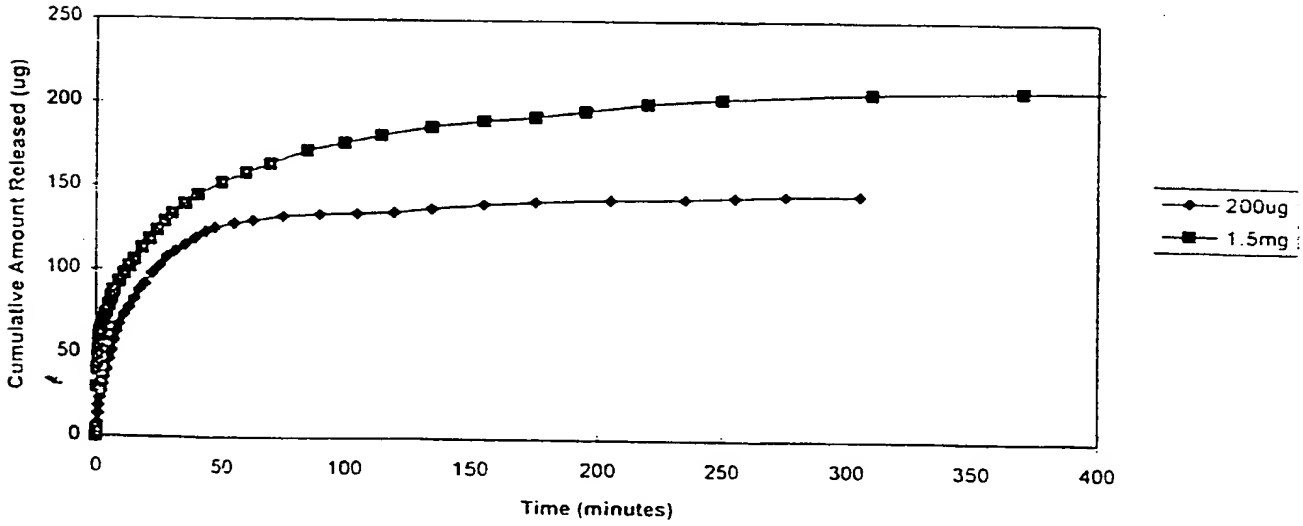

FIG. 4b

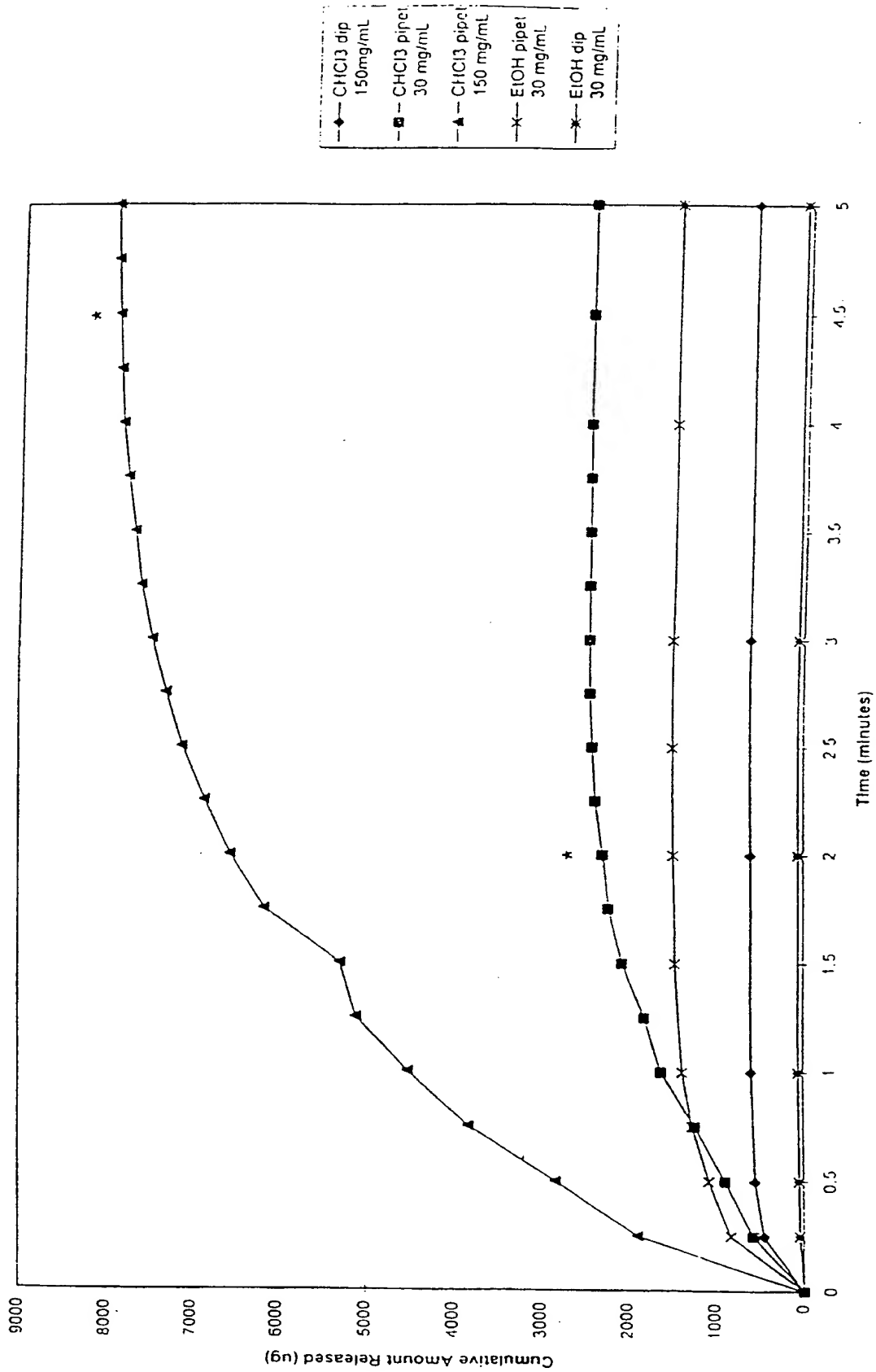

FIG. 5

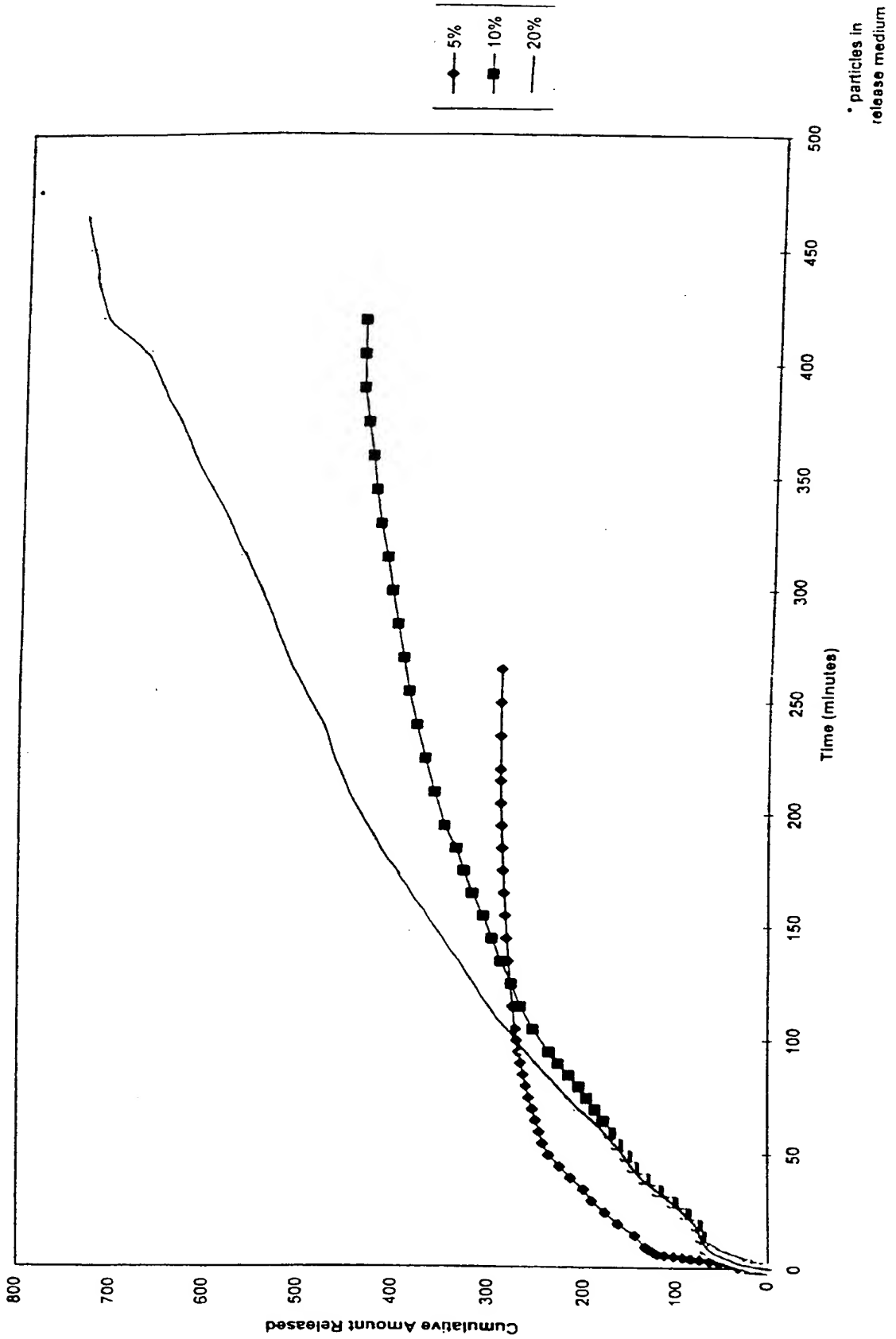

FIG. 6

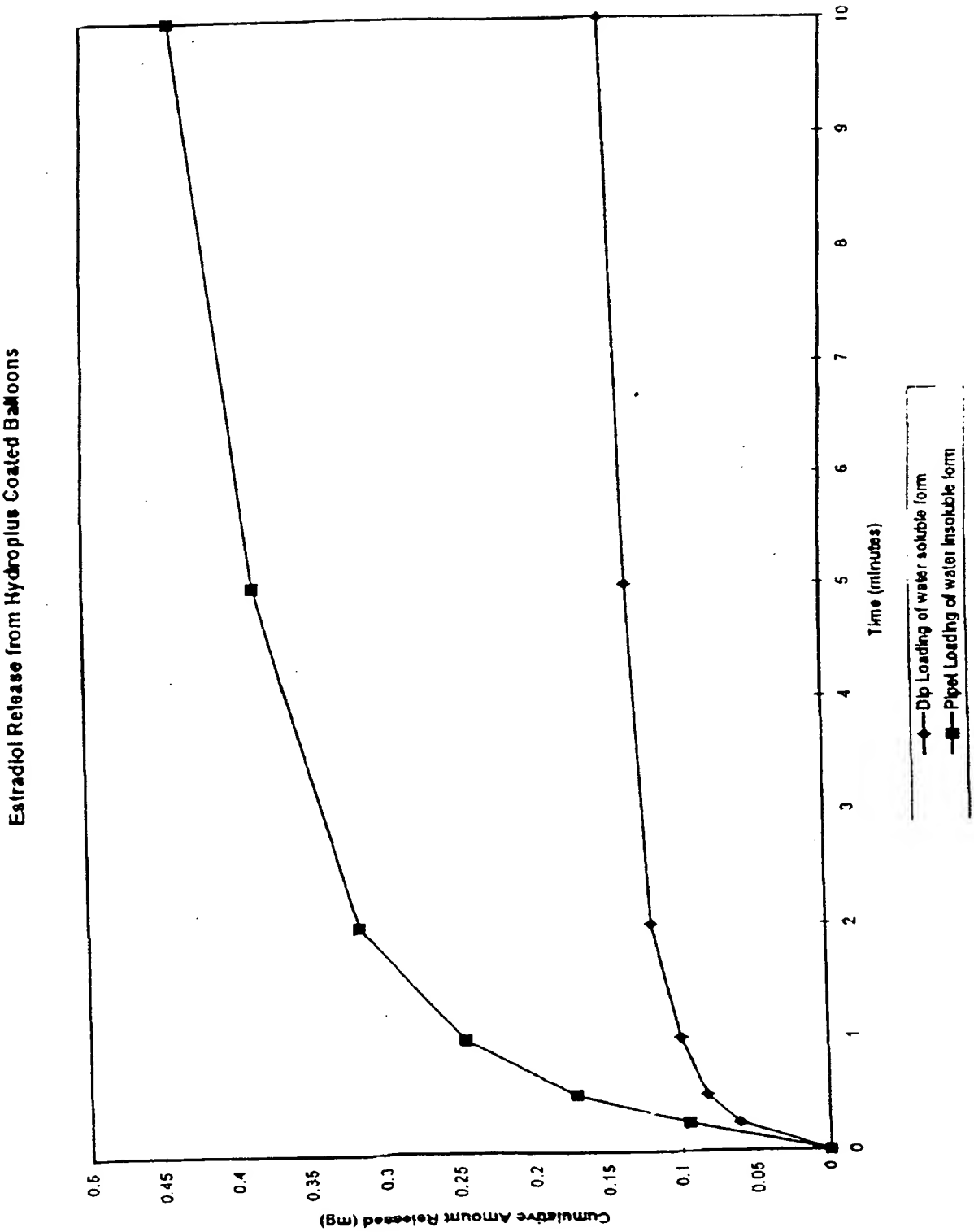

FIG. 7a

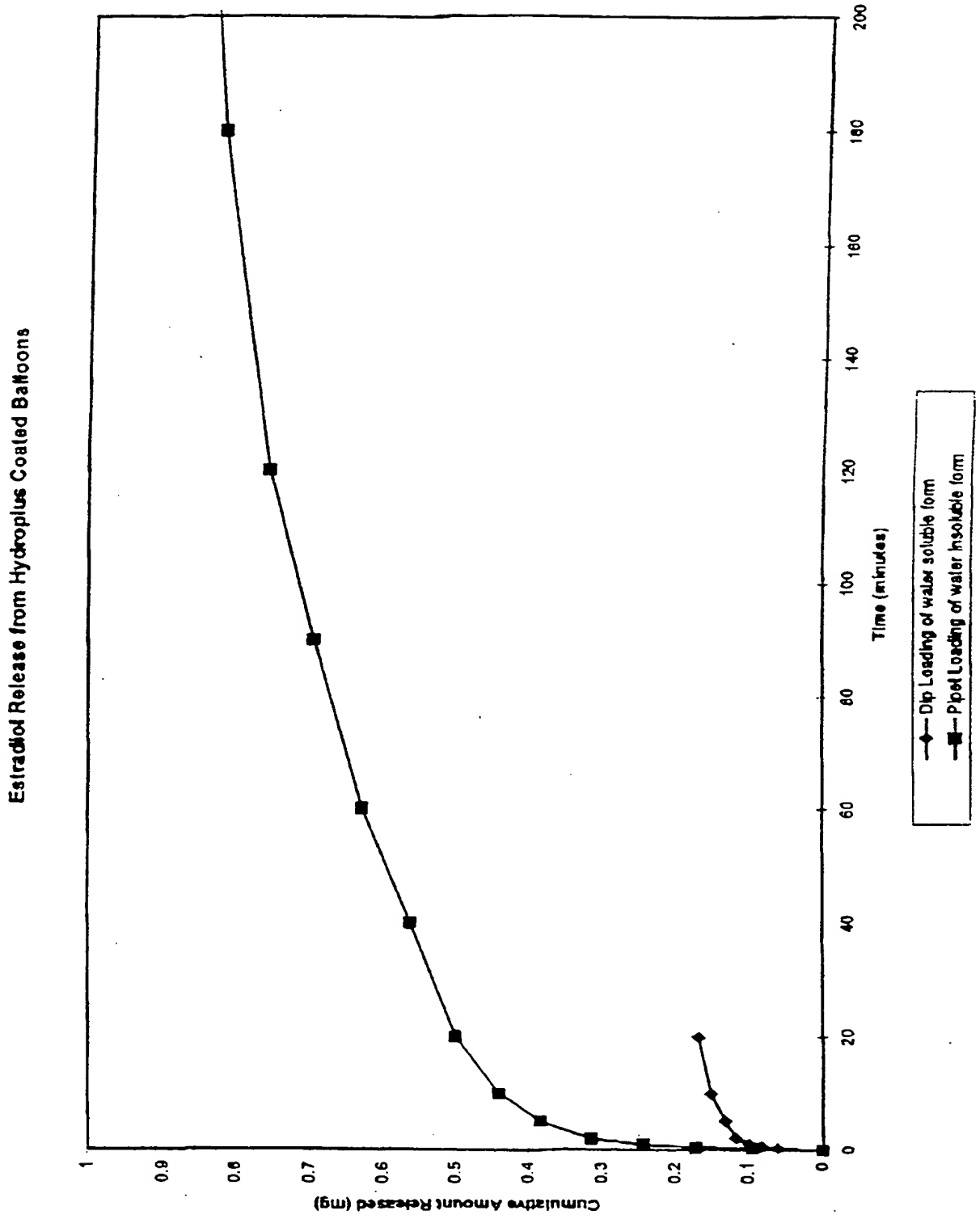

FIG. 7b

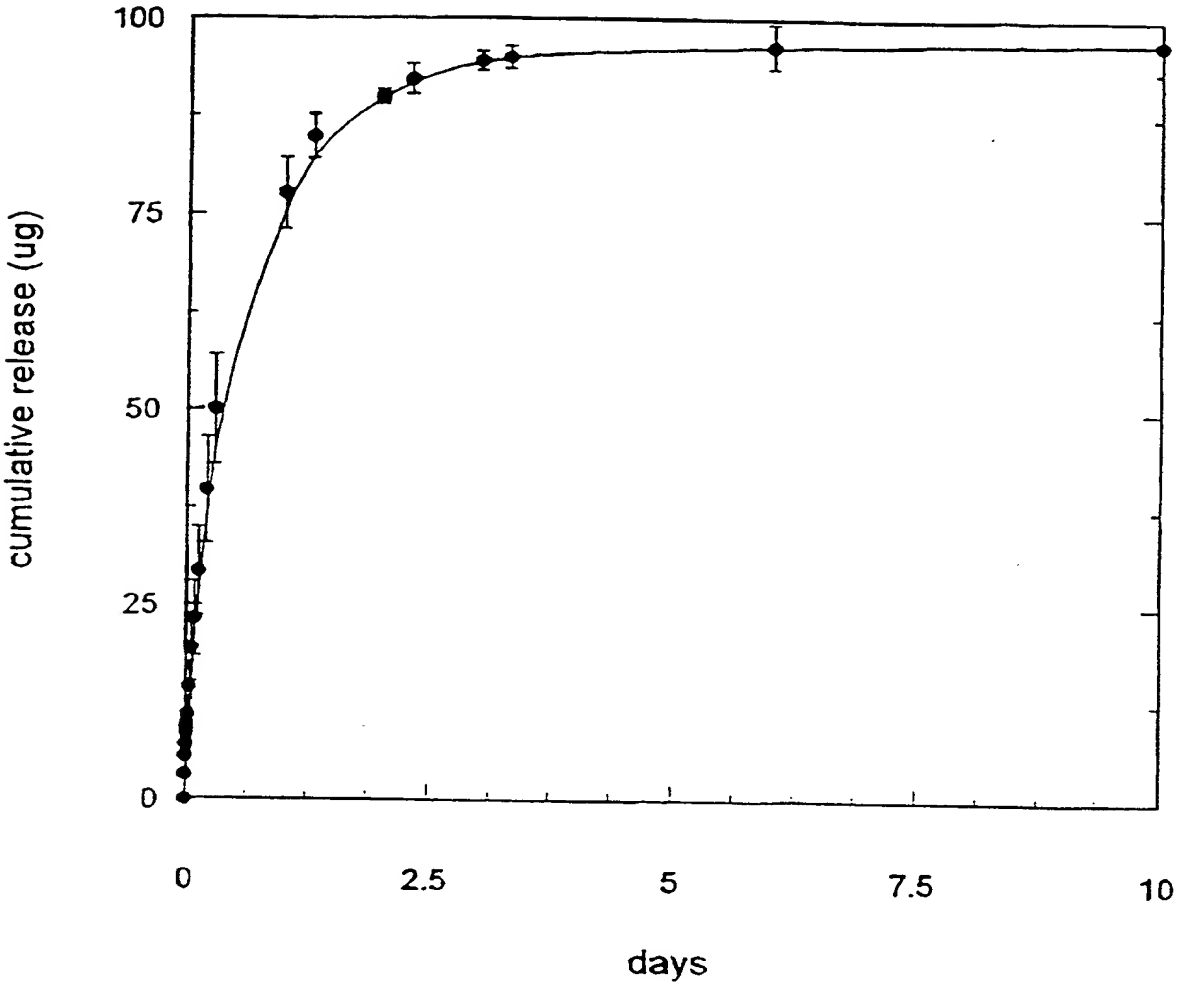

FIG. 8

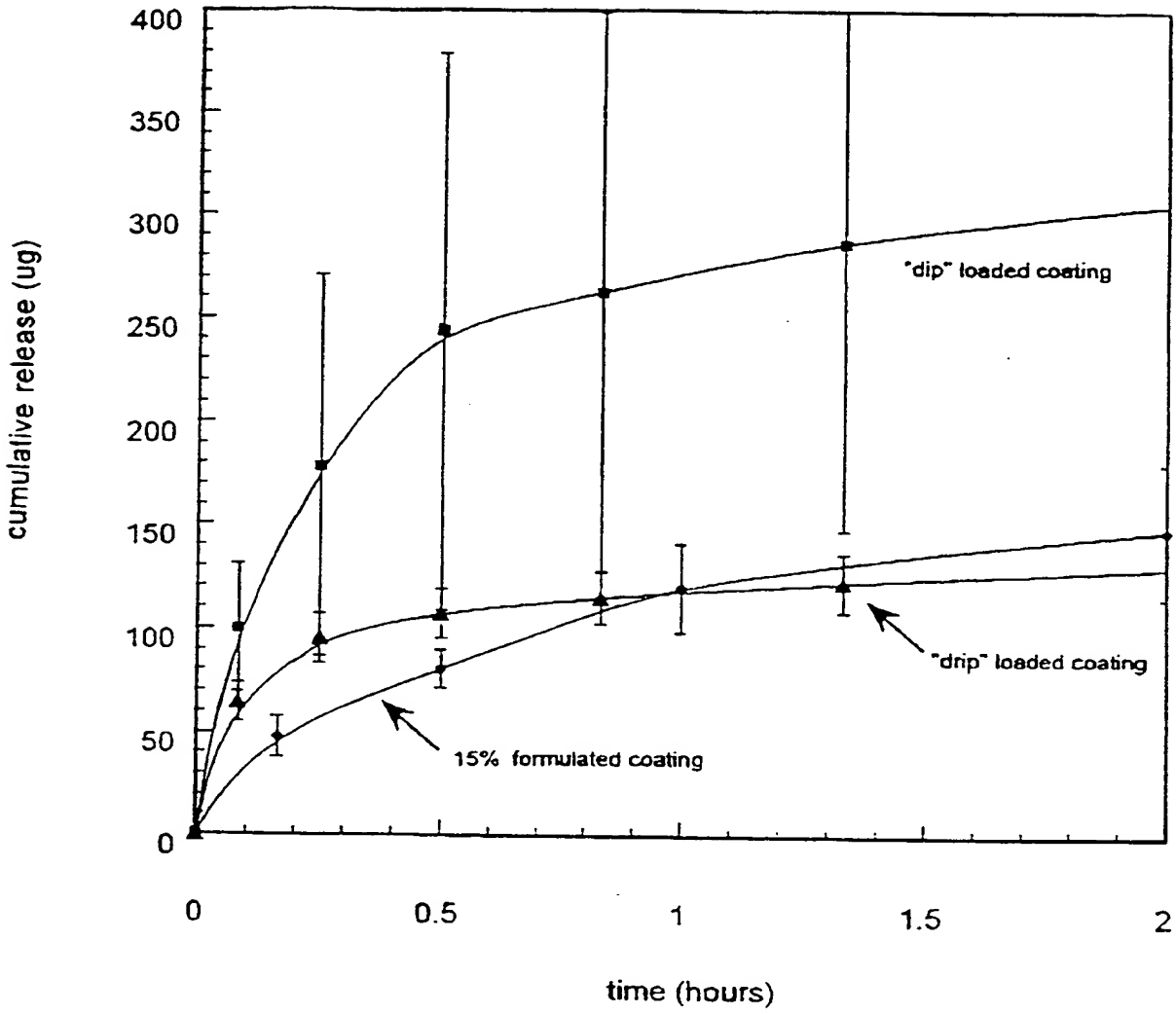

FIG. 9

INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/US 98/16775

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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27 November 1998	07/12/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A1

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(71) Applicant: BOSTON SCIENTIFIC CORPORATION [US/US]; One Boston Scientific Place, Natick, MA 01760–1537 (US).

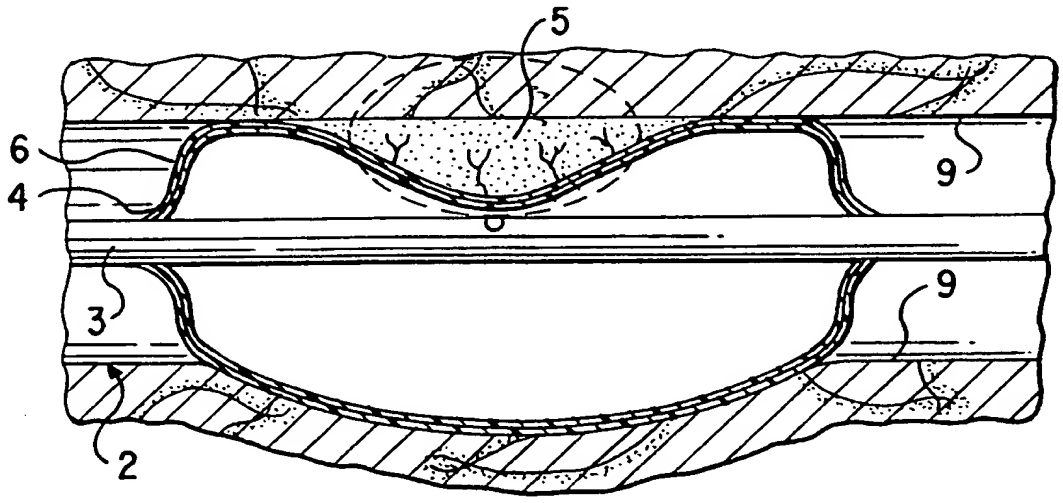
(72) Inventors: BARRY, James; 35 Jackson Circle, Marlboro, MA 01752 (US). PALASIS, Maria; 65 Martin Road, Wellesley, MA 02181 (US).

(74) Agents: BRAINARD, Charles, R. et al.; Kenyon & Kenyon, 1025 Connecticut Avenue, N.W., Washington, DC 20036 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: LOADING AND RELEASE OF WATER–INSOLUBLE DRUGS



(57) Abstract

A medical device, polymer composition, and method for delivering substantially water–insoluble drugs to tissue at desired locations within the body. At least a portion of the exterior surface of the medical device is provided with a polymer coating. Incorporated in the polymer coatings is a solution of at least one substantially water–insoluble drug in a volatile organic solvent. The medical device is positioned to a desired target location within the body, whereupon the drug diffuses out of the polymer coating.

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NSDOCID: <WO___9908729A1_IA>

LOADING AND RELEASE OF WATER-INSOLUBLE DRUGS

FIELD OF THE INVENTION

The invention relates to methods and devices for the localized delivery of substantially water-insoluble drug agents within the body.

BACKGROUND

The systemic administration of drug agents, such as by transoral or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because, for example, the drug agents may have unwanted effects on parts of the body which are not to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration.

It is therefore often desirable to administer drug agents at a localized site within the body. Common examples include cases of localized disease or occluded body lumens. Various methods have been proposed for such localized drug administration. For example, U.S. Patent No. 5,304,121, hereby incorporated by reference, discloses a method of delivering water-soluble drugs to tissue at desired locations of a body lumen wall. The method generally includes the steps of impregnating a hydrogel polymer on an expandable catheter with an aqueous drug solution, inserting the catheter into a blood vessel to a desired location, and expanding the catheter against the surrounding tissue allowing the release of the drug to the tissue. This method of localized drug delivery using hydrogel polymer impregnation has a limitation of being applicable to drug agents which are dissolved in water at concentrations

sufficient for therapeutic gel loading levels. There thus exists a need for a method and apparatus for the localized delivery of drug agents within the body, where the drug agents are substantially water-insoluble.

SUMMARY OF THE INVENTION

One objective of the present invention is to provide a method and apparatus for the localized delivery of substantially water-insoluble drug agents to predetermined locations within the human body.

A further objective of the present invention is to provide a method and apparatus to facilitate gradual, localized release of drug agents at predetermined locations within the human body.

A further objective of the invention is to administer drug agents by diffusion directly into the tissue requiring treatment. The drug is preferably applied in a manner that does not further injure the tissue to be treated, and administration is selectively and evenly distributed over the treated area such that the drug can be taken up by the tissue, without, for example, being washed away by body fluids.

The present invention provides methods and medical devices for the localized delivery of substantially water-insoluble drugs agents.

A particular embodiment of the present invention features a catheter and method for delivering substantially water-insoluble drug agents to tissue at a desired location along body lumen walls. The catheter is constructed for insertion in a body lumen and has a catheter shaft and an expandable portion mounted on the catheter shaft. The expandable portion is expandable to fill the cross-section of the body lumen. At least a portion of the exterior surface of the expandable portion is defined by a polymer coating. Incorporated into the polymer coating is at least one substantially water-insoluble drug. The catheter is positioned to a desired

target location within the body, whereupon the polymer coating absorbs water, thus dissolving the drug and resulting in the diffusion of the drug out of the polymer coating. The polymer and drug are selected to allow controlled release of a desired dosage of the drug from the polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1a shows one embodiment of the present invention in which a drug solution is impregnated into a polymer-coated balloon catheter.

Fig. 1b shows the insertion of a polymer-coated balloon catheter into a body lumen, in accordance with the present invention.

Fig. 1c shows the expansion of a polymer-coated balloon catheter at an occlusion site within a body lumen, in accordance with the present invention.

Fig. 2 shows a drug delivery balloon catheter embodiment of the present invention including a sheath for covering the catheter as it is being moved through a vessel toward the occlusion to be treated.

Figs. 3a and 3b show the release profile of paclitaxel from a balloon catheter having a polyacrylic acid-based coating for up to 50 and 5000 minutes, respectively, in accordance with the present invention.

Figs. 4a and 4b show the release profile of dexamethasone from a balloon catheter having a polyacrylic acid-based coating for up to 30 and 400 minutes, respectively, in accordance with the present invention.

Fig. 5 shows the release profiles of molsidomine from various balloon catheters having a polyacrylic acid-based coating for up to 5 minutes, in accordance with the present invention.

Fig. 6 shows the release profiles of dexamethasone from various balloon catheters having a polyacrylic acid-based coating for up to 450 minutes, in

accordance with the present invention.

Figs. 7a and 7b show the release profiles of water-soluble and substantially water-insoluble estradiol from balloon catheters having a polyacrylic acid-based coatings for up to 10 and 200 minutes, respectively, in accordance with the present invention.

Fig. 8 shows the release profile of paclitaxel for up to 10 days from polyurethane coated stents dipped in 30 mg/ml paclitaxel in ethanol for 3 days, in accordance with the present invention.

Fig. 9 shows the release profiles of paclitaxel from various polyurethane-coated balloon catheters for up to 2 hours, in accordance with the present invention.

DETAILED DESCRIPTION

The present invention provides methods and medical devices for the localized delivery of one or more substantially water-insoluble drug agents to predetermined locations within the human body.

In accordance with an embodiment of the invention, a substantially water-insoluble drug agent is dissolved in a volatile organic solvent. "Organic solvent" is intended to mean a singular organic solvent or a solvent mixture having at least one organic component. The solvent mixture also includes mixtures of water with miscible organic solvents. The drug solution is then applied to a polymer coating on a medical device that is adapted for insertion into the body. Examples of such medical devices include catheters, guide wires, balloons, filters (*e.g.*, vena cava filters), stents, stent grafts, vascular grafts, implants and other devices used in connection with drug-loaded polymer coatings.

In a preferred embodiment, the polymer is provided in the form of a coating on an expandable portion of a catheter. After applying the drug solution to the polymer and evaporating the volatile solvent from the polymer, the catheter is inserted into a body lumen

where it is positioned to a target location. The expandable portion of the catheter is subsequently expanded to bring the drug-impregnated polymer coating into contact with the lumen wall. The drug is released from the polymer as it slowly dissolves into the aqueous bodily fluids and diffuses out of the polymer. This enables administration of the drug to be site-specific, limiting the exposure of the rest of the body to the drug.

The polymer used in the present invention is preferably capable of absorbing a substantial amount of drug solution. When applied as a coating on a medical device in accordance with the present invention, the dry polymer is typically on the order of about 1 to 10 microns thick, preferably about 2 to 5 microns. Very thin polymer coatings, *e.g.*, of about 0.2-0.3 microns and much thicker coatings, *e.g.*, more than 10 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto a medical device. Such multiple layers are of the same or different polymer materials.

The polymer of the present invention is hydrophilic or hydrophobic, and is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. The preferred polymer is polyacrylic acid, available as HYDROPLUS (Boston Scientific Corporation, Natick, Mass.), and described in U.S. Pat. No. 5,091,205, the disclosure of which is hereby incorporated herein by reference. U.S. Patent No. 5,091,205 describes medical devices coated with one or more polyisocyanates such that

the devices become instantly lubricious when exposed to body fluids.

By "substantially water-insoluble drug" is meant any therapeutic agent having a greater solubility in organics than in water. More specifically, such drugs have a water solubility of no greater than 1 part drug to 30 parts water, more typically no greater than 1 part drug to 1,000 parts water. Such solubilities are described as "sparingly soluble" to "very slightly soluble" in the art.

The drug agents used in the present invention are selected from a number of drug types depending on the desired application. For example, these drugs include anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, and analogues thereof; antineoplastic/ antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, thymidine kinase inhibitors, and analogues thereof; anesthetic agents such as lidocaine, bupivacaine, ropivacaine, and analogues thereof; anti-coagulants; and growth factors.

In accordance with the present invention, the drug agents are dissolved in a volatile organic solvent such as, for example, ethanol, isopropanol, chloroform, acetone, pentane, hexane, or methylene chloride, to produce a drug solution. The drug solution is then applied to the polymer. A volatile organic solvent typically is selected to provide drug solubilities much greater than the corresponding aqueous solubility for the substantially water-insoluble drug. Accordingly, application of the drug solution to the polymer often results in drug loadings that are orders of magnitude greater than loadings that can be achieved by application of a saturated aqueous solution of the drug to the polymer.

The drug solution is applied to the polymer coating by any suitable means, including dipping the polymer coating into the drug solution or by applying the solution onto the coating such as by pipet. In the former method, the amount of drug loading is controlled by regulating the time the polymer is immersed in the drug solution, the extent of polymer cross-linking, the concentration of the drug in the solution and/or the amount of polymer coating. In another embodiment of the invention, the drug is incorporated directly into the polymer prior to the application of the polymer topcoat as a coating onto a medical device.

After applying the drug solution to the polymer coating, the volatile solvent is evaporated from the coating, for example, by drying in air or in an oven.

The release profile of the drug from the polymer coating is determined by many factors including the drug solubility, and the thickness and porosity of the polymer coating. When an expandable member such as a balloon catheter is used to administer the drug, pressure can be used to increase the rate of drug transfer to the tissue. An increase in pressure increases the diameter of the balloon and therefore the diameter of the surrounding tissue, thereby increasing the surface area for drug transfer. The amount of drug that is delivered per unit time is therefore increased.

When an expandable catheter is chosen as the medical device of the present invention, the expandable portion is preferably a balloon, in which case the drug is placed in the polymer for controlled release of the drug upon expansion of the balloon against a body lumen. The expandable portion optionally includes a stent, mountable in a body lumen by expansion thereof. The catheter also optionally comprises a sheath member which is extendable over the expandable portion to inhibit release of the drug into body fluids during placement of the catheter.

Referring now to Figs. 1a-1c, an embodiment for the localized delivery of substantially water-insoluble drugs to a predetermined location within the body is described. The drug administration method shown in Figs. 1a-1c illustrates the use of the present invention in conjunction with an angioplasty process. Catheter device 1 comprises a body 3 having a balloon 4 attached at its distal end. The balloon 4 on the catheter 3 includes a polymer coating 6. As shown in Fig. 1a, drug solution 8 is impregnated into the polymer coating with the balloon in its substantially deflated state prior to insertion into the patient. As shown in Fig. 1b, after the volatile solvent is evaporated, the device 1 is inserted into a body lumen 2 having a region to be treated, such as an occlusion due to a deposition of plaque 5 on the lumen wall tissue 9. The device 1 is moved along the vessel to position the balloon 4 at the occlusion site, as shown in Fig. 1c. The lumen may be, for example, a narrow, tortuous opening through which the catheter is passed by torquing or other known techniques. As shown in Fig. 1c, the balloon is inflated to provide close contact between the drug-impregnated polymer coating 6 and the surrounding plaque and tissue. As water from the body penetrates into the polymer coating 6, it begins to dissolve the drug agent, which subsequently diffuses out of the polymer coating 6 and into the surrounding plaque and tissue.

During drug administration, a substantial amount of the drug contained in the polymer coating is diffused into the affected area. The inflation pressure needed to expand the balloon catheter and dilate the lumen, if necessary, is typically in the range of about 1 to 20 atm. The balloon is formed of any suitable materials such as vinyl polymers such as polyethylene; polyesters such as polyethylene terephthalate; polyamides such as nylon; polyolefins and copolymers thereof (*e.g.*, Selar, Pebax, Surlyn, Hytrel, etc.). The balloon is

optionally a perfusion balloon, which allows blood to perfuse the catheter to prevent ischemia during delivery. A perfusion balloon is particularly preferred for long arterial delivery times and when the delivery drug is only very slightly soluble in water.

Referring to the embodiment of the invention illustrated in Fig. 2, the balloon portion 4 of catheter 3 is optionally covered by a protective sheath 7 while the instrument 1 is inserted into a body lumen 2 and positioned at a treatment region. As the coated balloon 4 is positioned at occluded site 5, the protective sheath 7 is drawn back to expose the balloon 4. In an alternative embodiment, the sheath remains stationary while the catheter moves the coated balloon forward into the occluded region. The sheath 7 protects the coating and inhibits premature release of the drug. Such a sheath might be particularly advantageous when using drugs which are not sufficiently water-insoluble or if even minor delivery to tissue during catheter placement is a problem, *e.g.* for extremely toxic drugs.

Although Figs. 1 and 2 illustrate the application of the present invention to an angioplasty process, the present invention is also used to administer drug agents to target locations where there is no occlusive formation.

Procedures for preparing a drug delivery balloon catheter with a polymer coating are presented in the following non-limiting examples.

Example 1: Release kinetics of paclitaxel from polyacrylic acid-based coating.

A 2 mg/ml solution of paclitaxel is prepared in chloroform. The solution is gently agitated until the paclitaxel is completely dissolved. The solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating and inflated to 2 atm. A total of 100 μl of solution, and hence 200 μg of

paclitaxel, is applied to the catheter. The balloon catheter is then dried in air for 30 minutes and in a vacuum oven for 48 hours at 50°C to evaporate the chloroform. The catheter is then immersed in a solution of 1% dimethyl sulfoxide (DMSO) and phosphate buffered saline(PBS) having a pH of 7.4 for in-vitro drug release. The cumulative amount of paclitaxel released from the catheter coating yields the data shown in Figs. 3a and 3b.

Example 2: Release kinetics of dexamethasone from polyacrylic acid-based coating.

Solutions containing 1.5 mg/ml and 200 μg/ml of dexamethasone in chloroform, are prepared by gently agitating until the dexamethasone is completely dissolved. The solutions are separately applied via dripping to separate balloon catheters having polyacrylic acid-based coatings and inflated to 2 atm. A total of 100 μl of each solution is applied to each respective catheter, corresponding to dexamethasone loadings of 150 μg and 20 μg, respectively. These results can be contrasted with the inability to apply substantial amounts of dexamethasone to polyacrylic acid-based coatings using aqueous solutions, in which case only about 1 μg of dexamethasone can be loaded into such coatings. The balloon catheters are then dried in a vacuum oven for 2 hours at 50°C to evaporate the chloroform solvent. The catheters are thereafter immersed in PBS (pH = 7.4) to track the release of dexamethasone over time. The cumulative amount of dexamethasone released from each catheter yields the data shown in Figs. 4a and 4b.

Example 3: Release kinetics of molsidomine from polyacrylic acid-based coating.

Various solutions of molsidomine in volatile solvents are prepared and applied to balloon catheters by

the methods indicated in Table I. In the "dip" application technique, each balloon catheter having a polyacrylic acid-based coating is dipped into its respective solution for 10 minutes. In the "pipet" application technique, 200 μl of solution is pipetted onto its respective coated balloon catheter while slowly turning. All samples are dried in an oven for 30 minutes at 50°C and thereafter immersed in PBS (pH = 7.4) to track the release of molsidomine over time. The cumulative amount of molsidomine released from each catheter yields the data shown in Fig. 5a and 5b.

Table I. Molsidomine solution characterization, and methods of applying molsidomine solution to polymer coated catheters.

Sample	Solvent	Concentration (mg Molsidomine per ml solvent)	Application technique
1	chloroform	150	dip
2	chloroform	30	pipet
3	chloroform	150	pipet
4	ethanol	30	pipet
5	ethanol	30	dip

Example 4: Release kinetics of dexamethasone added to polyacrylic acid-based topcoat formulation.

Rather than forming a solution of dexamethasone in an organic solvent and then applying this solution to polymer-coated balloon catheters as in Example 2, dexamethasone is added directly to the polymer used to coat the balloon catheters. Dexamethasone is weighed out into 0.05 g, 0.1 g, and 0.2 g samples, each of which is each added to 1 ml lots of polymer topcoat solution containing polyacrylic acid, methyl ethyl ketone, dimethyl formamide, and t-butyl alcohol. The dexamethasone samples are mixed with the polymer topcoat

solutions until completely dissolved. The dexamethasone-containing polymer topcoat solutions are separately applied via dripping to separate, uncoated balloon catheters inflated to 2 atm. After drying in a vacuum oven for 2 hours at 50°C, the catheters are immersed in PBS (pH = 7.4) to track the release of dexamethasone over time. The cumulative amount of dexamethasone released from each catheter yields the data shown in Fig. 6.

Example 5: Comparative release kinetics for water-soluble and water-insoluble estradiol.

Estradiol is provided in both water-soluble and substantially water-insoluble forms. Water-soluble estradiol is applied to a balloon catheter coated with a polyacrylic acid-based coating by i) preparing a 10 mg/ml solution of water-soluble estradiol in deionized, ultra-filtered water; and ii) placing the balloon catheter, inflated to 2 atm, into 200 μl of the solution for 20 minutes. Water-insoluble estradiol is applied to a balloon catheter coated with a polyacrylic-acid based coating by i) preparing a 10 mg/ml solution of substantially water-insoluble estradiol in methanol; and ii) dripping 100 μl of the solution onto the balloon catheter. The catheters are thereafter immersed in PBS (pH = 7.4) to track the release of both water-soluble and water-insoluble estradiol over time. Greater release is observed for the substantially water-insoluble form of estradiol when compared to the water-soluble form. The cumulative amount of estradiol released from each catheter yields the data shown in Figs. 7a and 7b.

Example 6: In-vivo delivery of paclitaxel from polyacrylic acid-based coating.

A 9.8 mg/ml solution of radio-labeled paclitaxel in chloroform is prepared. A total of 50 μl of the solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating. The

paclitaxel from the coated balloon catheter is then released in-vivo to porcine arteries. After release for a predetermined amount of time, the paclitaxel remaining in the coating is extracted using two sequential ethanol washes. The amount of paclitaxel released in the pig bloodstream, as calculated from the amount of paclitaxel loaded into the coating minus that extracted from the coating after delivery, is shown in Table II.

Table II. Amount of paclitaxel released into pig bloodstream from an impregnated, polyacrylic acid-based coated balloon catheter, as a function of delivery time.

Amount of time in bloodstream	Amount of paclitaxel extracted from balloon after delivery (μg)	Amount of paclitaxel released in bloodstream (μg)	% of paclitaxel released in bloodstream
1 minute	182 ± 1	307	63
5 minutes	160 ± 30	330	68

Example 7: Delivery of paclitaxel to explanted porcine arteries from polyacrylic acid-based coating.

A 9.8 mg/ml solution of radio-labeled paclitaxel in chloroform is prepared. A total of 50 μl of the solution is applied via pipet to a balloon catheter having a polyacrylic acid-based coating. The coated balloon catheter is then delivered to an explanted porcine artery for 15 minutes. After delivery, the paclitaxel remaining in the coating is extracted using two sequential ethanol washes. The delivered paclitaxel is extracted from the vessel, also by using two sequential ethanol washes. In addition, the vessel is placed in tissue solvent and counted for paclitaxel. Using these extraction methods, at least 80% of the paclitaxel loaded onto the balloon catheter is recovered, as shown in Table III.

Table III. Paclitaxel recovery from ex vivo delivery to porcine artery.

Amount paclitaxel loaded onto balloon	489 μg
Amount paclitaxel extracted from the balloon after delivery	360 μg
Amount paclitaxel extracted from artery	30 μg
Amount paclitaxel counted from tissue solution	1 μg
Total paclitaxel measured	391 μg
Percentage of paclitaxel recovered	80%

Example 8: Release kinetics of paclitaxel from polyurethane-based stent coating.

Slotted tube stainless steel stents are coated with polyurethane by spraying a 1 wt% solution of CHRONOFLEX polyurethane (made by CT Biomaterials) in tetrahydrofuran directly onto the stent surface. The coated stents are dried in a vacuum oven for three hours at 70°C.

Each polyurethane coated stent is placed in a vial, which is filled to maximum volume (1.5 ml) with a solution of paclitaxel in ethanol, and sealed. The stent is stored in the vial for three days at room temperature. The stent is then removed from the vial and dried for one hour at 65°C.

The above procedure is conducted using solutions of varying concentrations. Each stent is analyzed for paclitaxel content by extraction in dichloromethane solvent. The results are presented in Table IV below. Samples 1 and 2 were obtained using a paclitaxel concentration of 10 mg/ml, samples 3 and 4 using a 20 mg/ml solution and sample 5 and 6 using a 30 mg/ml solution.

Table IV. Paclitaxel content.

Sample #	Paclitaxel conc. (mg/ml)	Paclitaxel content (μg)	Coating Wt. (μg)	μg Paclitaxel per μg coating
1	10	44.8	796	0.06
2	10	88.2	859	0.10
3	20	151.2	718	0.21
4	20	127.6	702	0.18
5	30	157.1	736	0.21
6	30	144.3	629	0.23

These results suggest that Paclitaxel loading is relatively independent of paclitaxel concentration above 20 mg/ml, assuming equilibrium is attained in the three-day period. Nevertheless, the 30 mg/ml paclitaxel concentration is chosen for release studies as it produces the maximum paclitaxel loading (21-23%), while still being sufficiently below the saturation concentration for paclitaxel in ethanol (39 mg/ml).

Seven polyurethane coated stents are loaded using a 30 mg/ml paclitaxel solution, removed and dried as set forth above. Paclitaxel from four of the stents is extracted in dichloromethane solvent. The results of this extraction are presented in Table V below:

Table V. Paclitaxel content.

Sample #	Paclitaxel conc. (mg/ml)	Paclitaxel content (μg)	Coating Wt. (μg)	μg Paclitaxel per μg coating
1	30	111.7	676	0.17
2	30	50	627	0.08
3	30	45.3	612	0.07
4	30	37.4	602	0.06

The remaining three stents are immersed in a

solution of phosphate buffered saline solution having pH 7.4 at 37°C. Cumulative release as a function of time is presented in Fig. 8.

Example 9: Release kinetics of paclitaxel from polyurethane-based balloon catheter coating.

Nylon balloons are coated with polyurethane by dipping into a 9 wt% solution of CHRONOFLEX polyurethane in dimethylacetamide. The balloons are dried in a vacuum oven overnight at 50°C.

Each polyurethane coated balloon is loaded with paclitaxel either by dipping the coated balloon into a paclitaxel and ethanol solution or by dripping a known volume of a paclitaxel and ethanol solution onto the balloon surface.

In the first instance, a stock saturated solution of paclitaxel in ethanol is prepared. Then the polyurethane-coated balloon is inflated and submerged in the paclitaxel stock solution in a tube. The tube and balloon are well-sealed to prevent solvent evaporation. After remaining in the tube overnight, the ethanol is evaporated from the balloon over a suitable time period, such as about fifteen minutes. Five "dip-coated" balloons are prepared in this fashion.

In the second instance, a stock solution of paclitaxel having a concentration of 10 mg/ml prepared. Twenty ml of this paclitaxel stock solution are then pipetted onto an inflated polyurethane-coated balloon, providing a total mass of 200 mg of paclitaxel per balloon. Afterwards, ethanol is evaporated from the balloon over a suitable time period, such as about fifteen minutes. Five "drip-coated" balloons are prepared in this fashion.

Two drip-loaded balloons and two dip-loaded balloons are taken and the paclitaxel extracted in dichloromethane to determine total paclitaxel content. The paclitaxel content of the dip-coated balloons is

found to be 1093 +/- 439 μg, while the drip-coated balloons are found to have 215 +/- 11 μg paclitaxel.

For comparison, nylon balloons are coated with paclitaxel/polyurethane by dipping the balloons into a dispersion of 14.5 wt% BAYHYDROL polyurethane (made by Bayer) and 2.6 wt% paclitaxel in a mixture of 73.6 vol% N-methylpyrrolidinone and 26.4 vol% water. Balloons are dried in a vacuum oven overnight at 50°C. The dried coatings contain 15% paclitaxel by weight. Nine balloons are formed. Seven balloons are tested for paclitaxel loading yielding an average of 196 +/- 44 μg paclitaxel after extraction in dichloromethane.

The remaining three drip-loaded balloons from above, the remaining three dip-loaded balloons from above, and the remaining two balloons with the 15% paclitaxel formulated coating are placed in a solution of phosphate buffered saline solution having pH 7.4 at 37°C, and cumulative paclitaxel release is measured as a function of time. The results of this study are presented in Fig. 9.

It is to be appreciated that the parameters described in the above examples are merely illustrative and that the present invention is not limited to such parameters. For example, in each of the examples provided, any suitable polymer may be used for the polymer coating, any suitable drying time periods and temperatures may be used, any suitable organic solvent may be used, any suitable method for applying the polymer coatings to the medical devices may be used, any suitable method for applying the drugs to the polymer coatings may be used, any suitable water-insoluble analogue of the disclosed drugs may be used, and any suitable drug loading concentrations may be used.

The present invention provides a previously unknown method and medical device for the localized delivery of substantially water-insoluble drugs. Those

with skill in the art may recognize various modifications to the embodiments of the invention described and illustrated herein. Such modifications are meant to be covered by the spirit and scope of the appended claims.

We claim:

1. A method comprising the steps of:

providing a polymer;

providing a medical device adapted for insertion in a body;

coating at least a portion of the exterior surface of the medical device with the polymer to form a polymer coating; and

applying a drug solution to the polymer, said drug solution comprising at least one substantially water-insoluble drug dissolved in an organic solvent.

2. The method of claim 1, further comprising the step of drying said polymer coating such that substantially all of said solvent is evaporated.

3. The method of claim 1, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

4. The method of claim 3, wherein said polymer is polyacrylic acid.

5. The method of claim 1, wherein said at least one substantially insoluble drug is selected from the

group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

6. The method of claim 1, wherein said organic solvent is selected from the group consisting of ethanol, isopropanol, chloroform, acetone, pentane, hexane, methylene chloride, and mixtures thereof.

7. The method of claim 6, wherein said organic solvent includes water.

8. The method of claim 1, wherein said step of applying a drug solution to said polymer includes the step of dipping said polymer into said drug solution.

9. The method of claim 1, wherein said drug solution is applied to said polymer before said polymer is coated onto said medical device.

10. The method of claim 1, wherein said drug solution is applied to said polymer after said polymer is coated onto said medical device.

11. The method of claim 1, wherein said medical device is selected from catheters, guide wires, balloons, filters, stents, vascular grafts, and implants.

12. The method of claim 11, wherein said medical device is a catheter comprising a shaft and an expandable portion mounted on said shaft, at least a portion of the exterior surface of the expandable portion being covered with said polymer coating.

13. The method of claim 1, further comprising positioning

said medical device at a desired location in a body lumen.

14. The method of claim 13, wherein said medical device is a catheter comprising a shaft and an expandable portion mounted on said shaft, at least a portion of the exterior surface of the expandable portion being covered with said polymer coating.

15. The method of claim 14, further comprising the step of expanding said expandable portion of said catheter.

16. The method of claim 15, wherein said catheter comprises a sheath member which is extendable over said expandable portion.

17. The method of claim 16, further comprising the steps of:

extending said sheath over said expandable portion prior to said positioning; and

exposing said expandable portion from said sheath prior to said expanding.

18. The method of claim 1, wherein said step of coating comprises the step of applying multiple layers of said polymer to said medical device.

19. A medical device for delivering a substantially water-insoluble drug at a desired location within a body, comprising:

a medical device adapted for insertion in a body; and

a polymer coating containing at least one substantially water-insoluble drug provided on at least a portion of said medical device, wherein said substantially water-insoluble drug has a water-solubility no greater than 1 part drug to 30 parts water.

20. The medical device of claim 19, wherein said drug has a water solubility no greater than 1 part drug to 1,000 parts water.

21. The medical device of claim 20, wherein said medical device is a catheter for delivering substantially water-insoluble drugs to a desired location within a body lumen, said catheter comprising:

a shaft;

an expandable portion mounted on said shaft; and

a polymer coating on at least a portion of said expandable portion of said catheter, said polymer coating being impregnated with at least one substantially water-insoluble drug.

22. The medical device of claim 21, wherein said expandable portion includes an inflatable balloon.

23. The medical device of claim 22, further comprising a sheath member extendable over said expandable portion.

24. The medical device of claim 19, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane

dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

25. The medical device of claim 24, wherein said polymer is polyacrylic acid.

26. The medical device of claim 19, wherein said at least one substantially water-insoluble drug is selected from the group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

27. The medical device of claim 21, wherein said expandable portion includes a stent.

28. The medical device of claim 19, wherein said polymer coating is layered.

29. A polymer containing at least one substantially water-insoluble drug.

30. The polymer of claim 29, wherein said polymer is selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

31. The polymer of claim 30, wherein said polymer is polyacrylic acid.

32. The polymer of claim 29, wherein said at least one substantially water-insoluble drug is selected from the

group consisting of dexamethasone, molsidomine, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, paclitaxel, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, lidocaine, bupivacaine and ropivacaine.

33. The method of claim 1, wherein said polymer is polyurethane.

34. The method of claim 1, wherein said medical device is a stent.

35. The method of claim 1, wherein said drug is paclitaxel.

36. The method of claim 1, wherein said medical device is a stent, said polymer is polyurethane, and said drug is paclitaxel.

37. The medical device of claim 19, wherein said polymer is polyurethane.

38. The medical device of claim 19, wherein said medical device is a stent.

39. The medical device of claim 19, wherein said drug is paclitaxel.

40. The medical device of claim 19, wherein said medical device is a stent, said polymer is polyurethane, and said drug is paclitaxel.

41. The polymer of claim 29, wherein said polymer is polyurethane.

42. The polymer of claim 29, wherein said drug is paclitaxel.

43. The polymer of claim 29, wherein said polymer is polyurethane and said drug is paclitaxel.

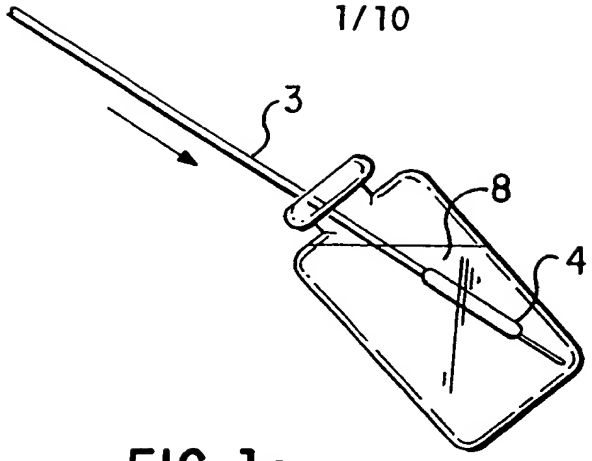

FIG. 1a

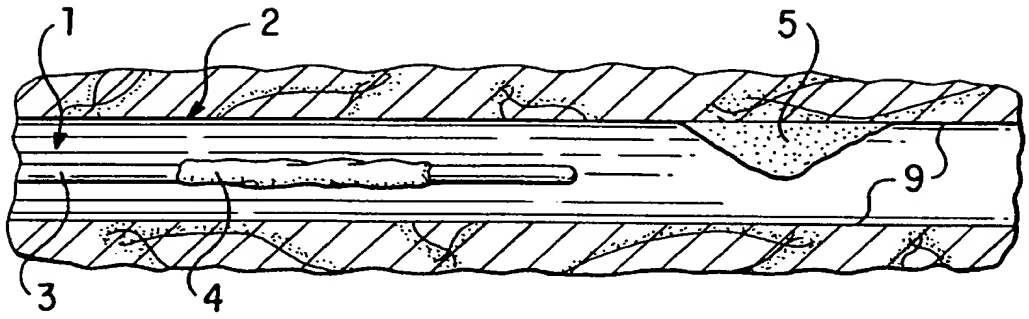

FIG. 1b

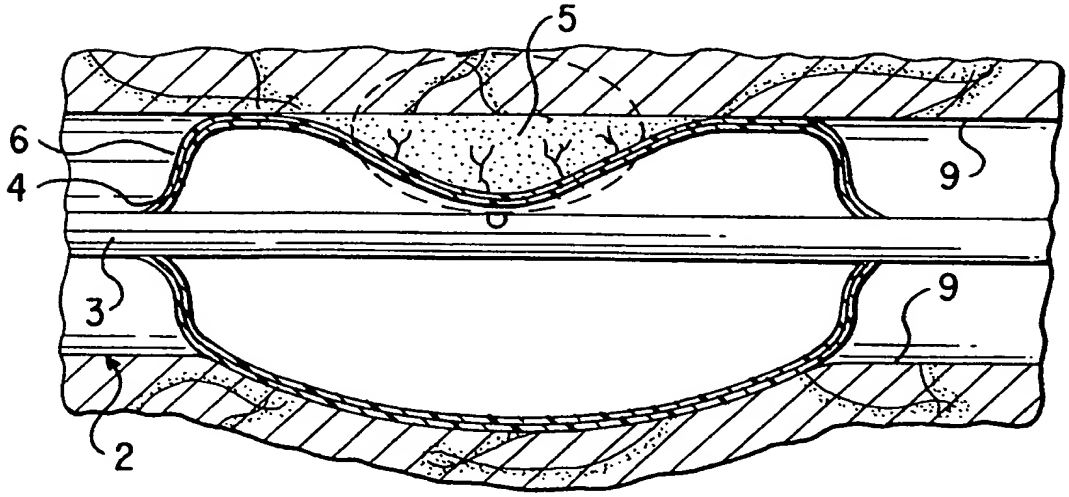

FIG. 1c

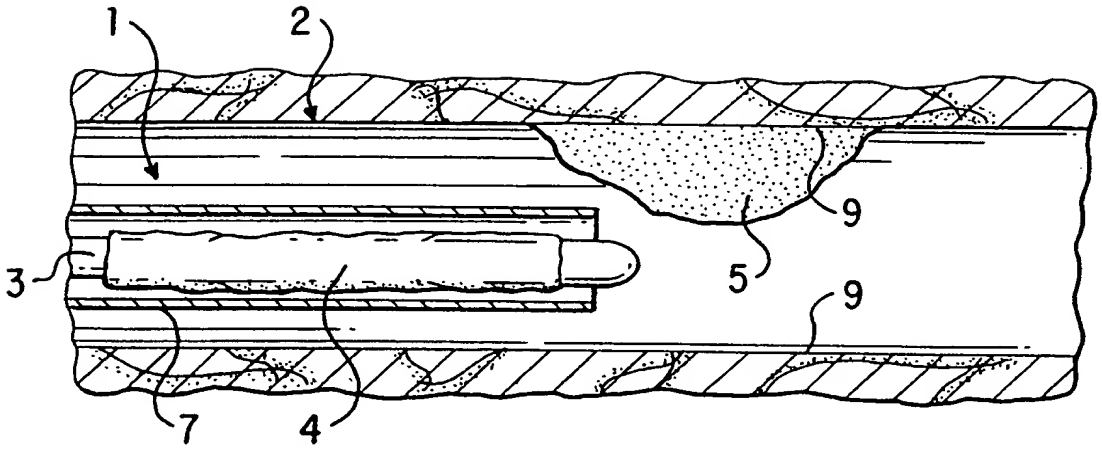

FIG. 2a

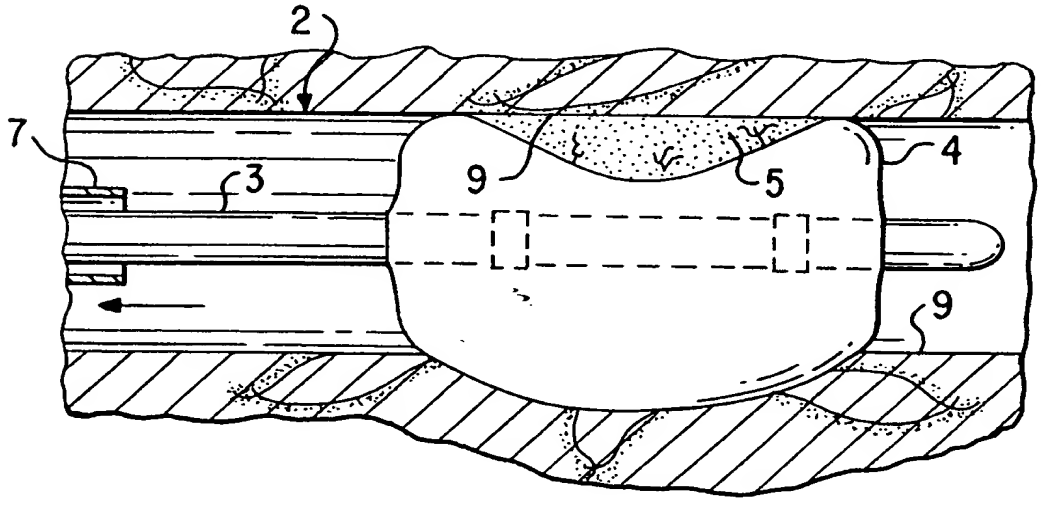

FIG. 2b

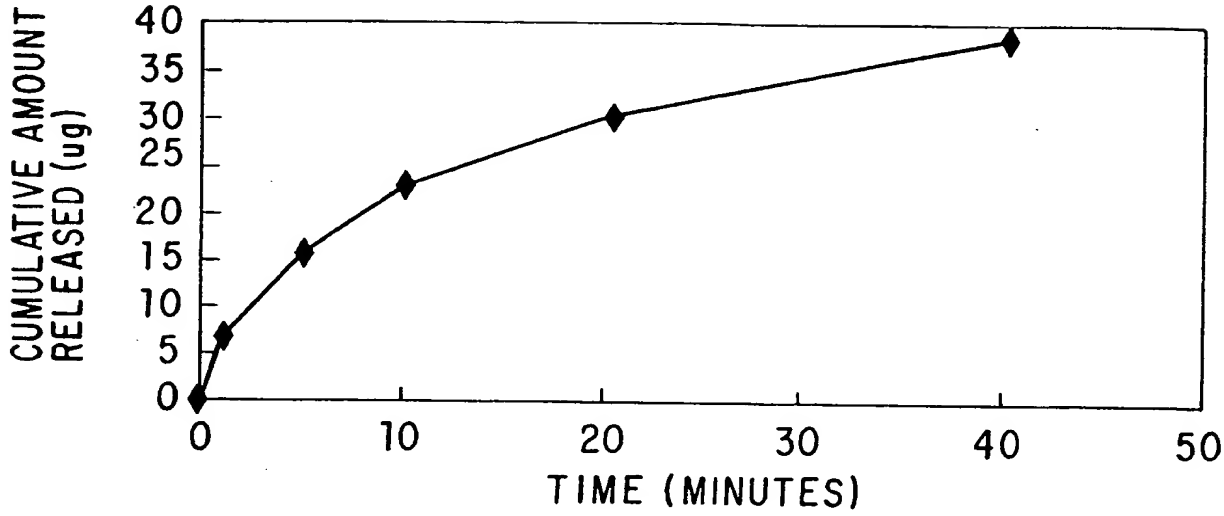

FIG. 3a

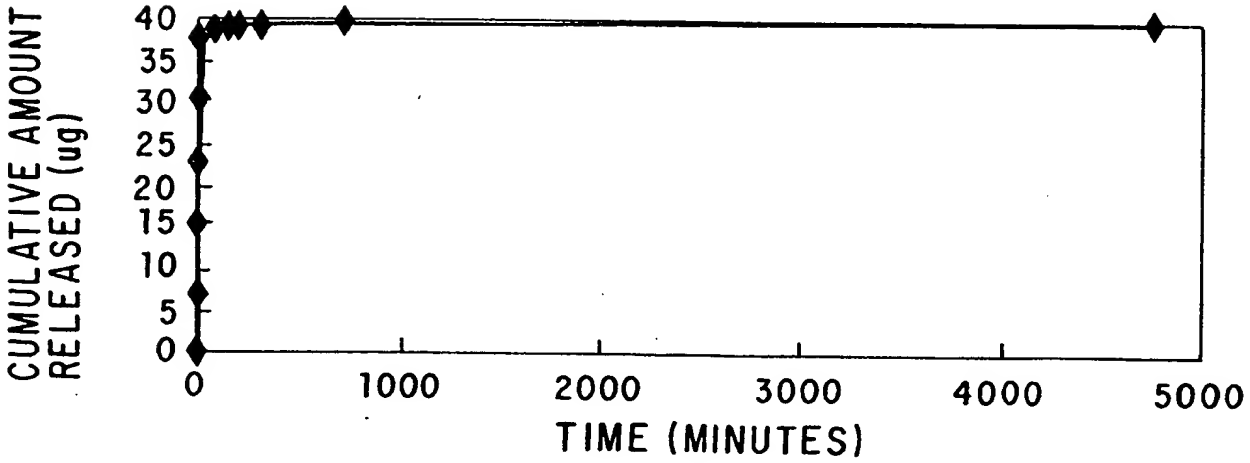

FIG. 3b

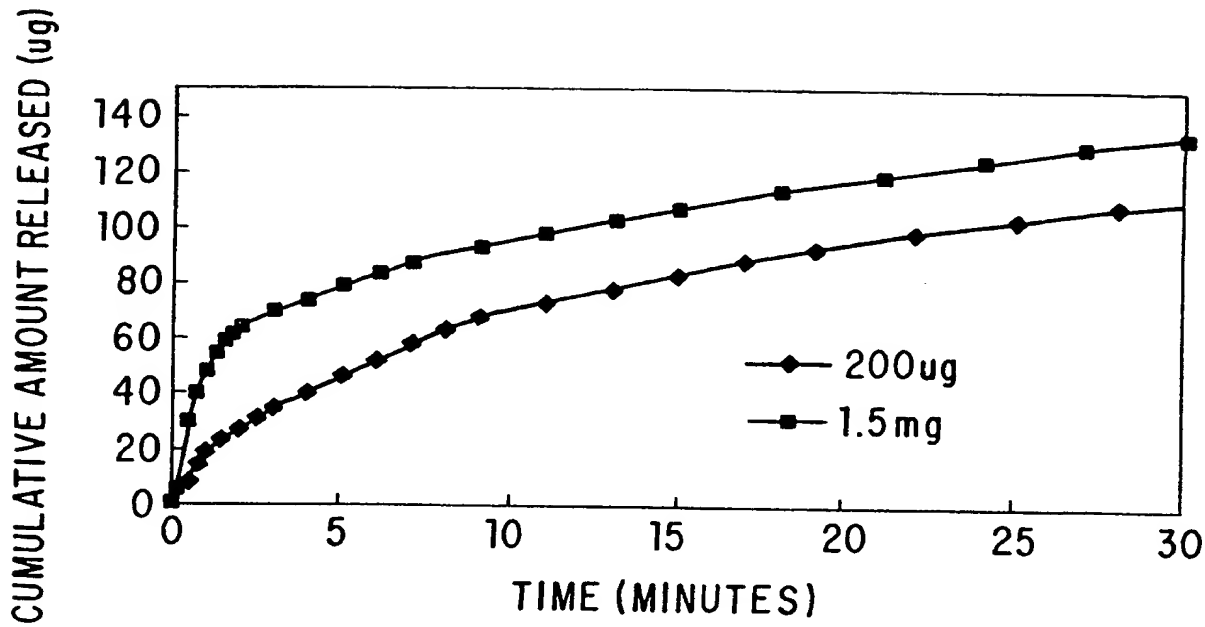

FIG. 4a

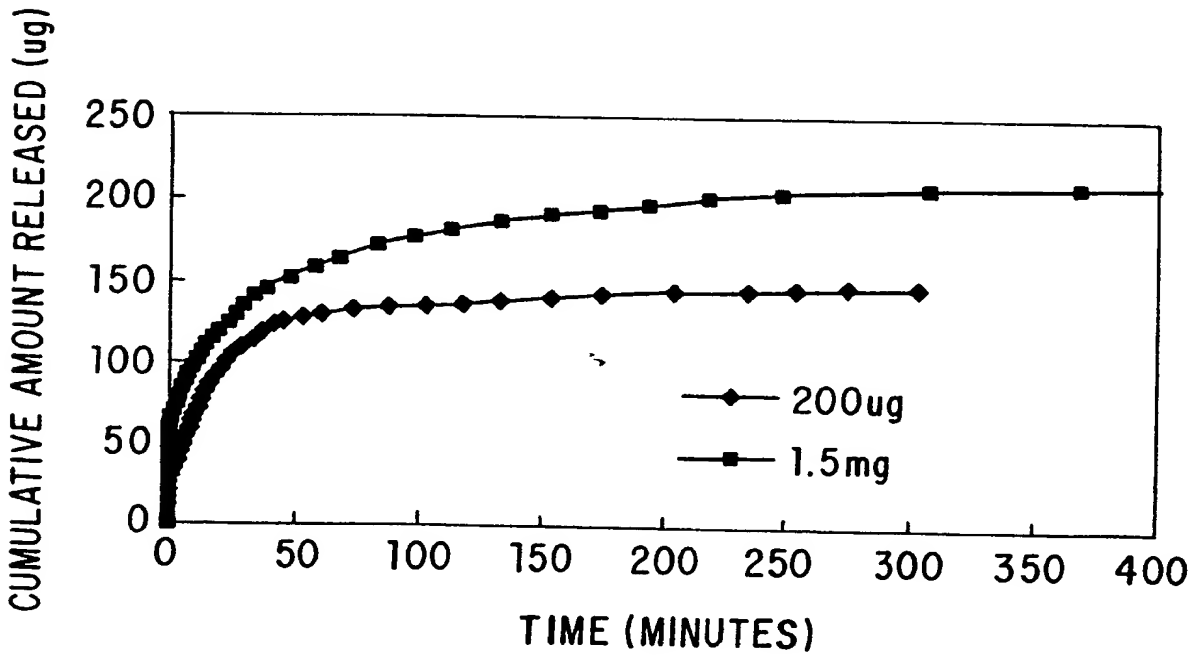

FIG. 4b

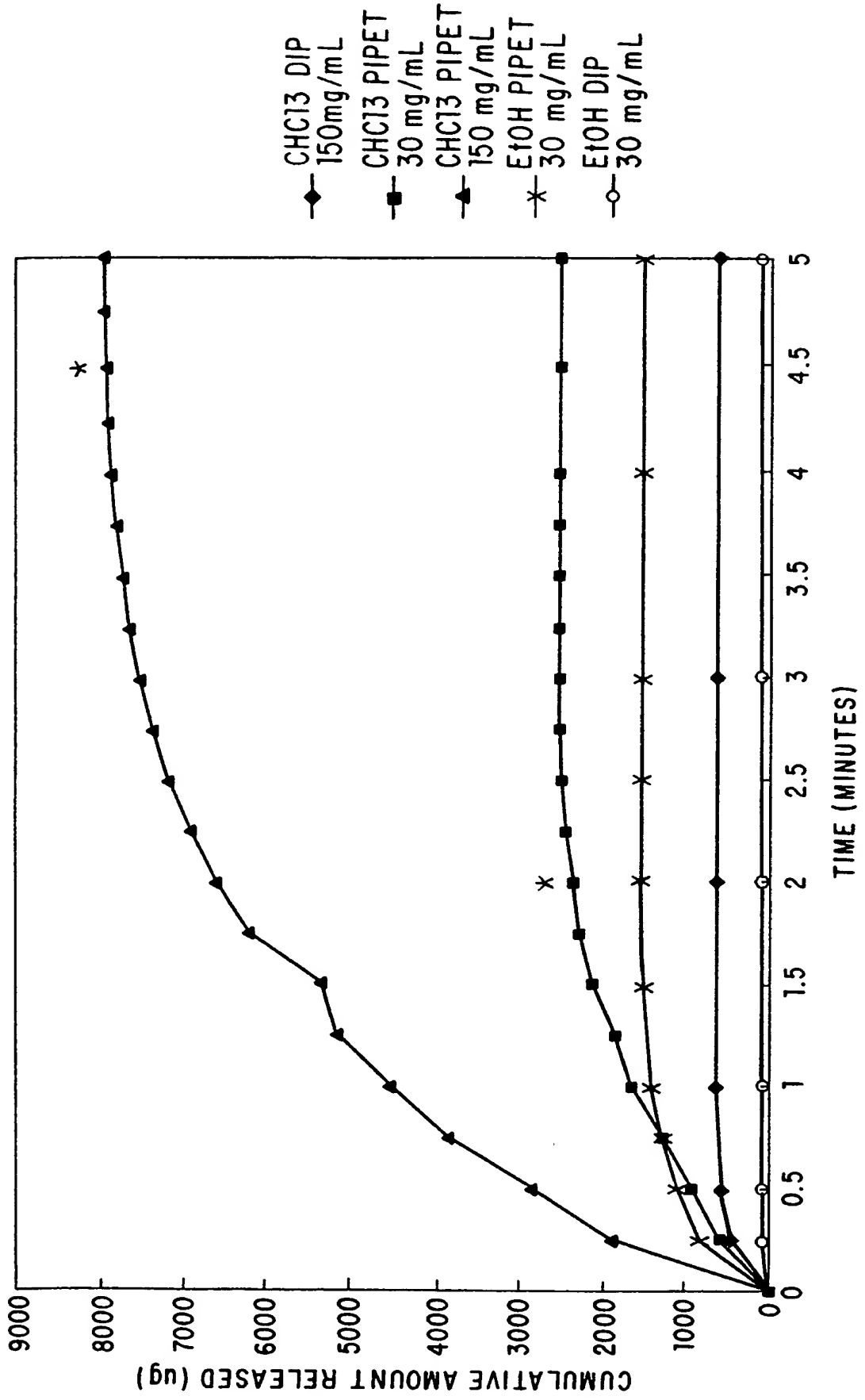

FIG. 5

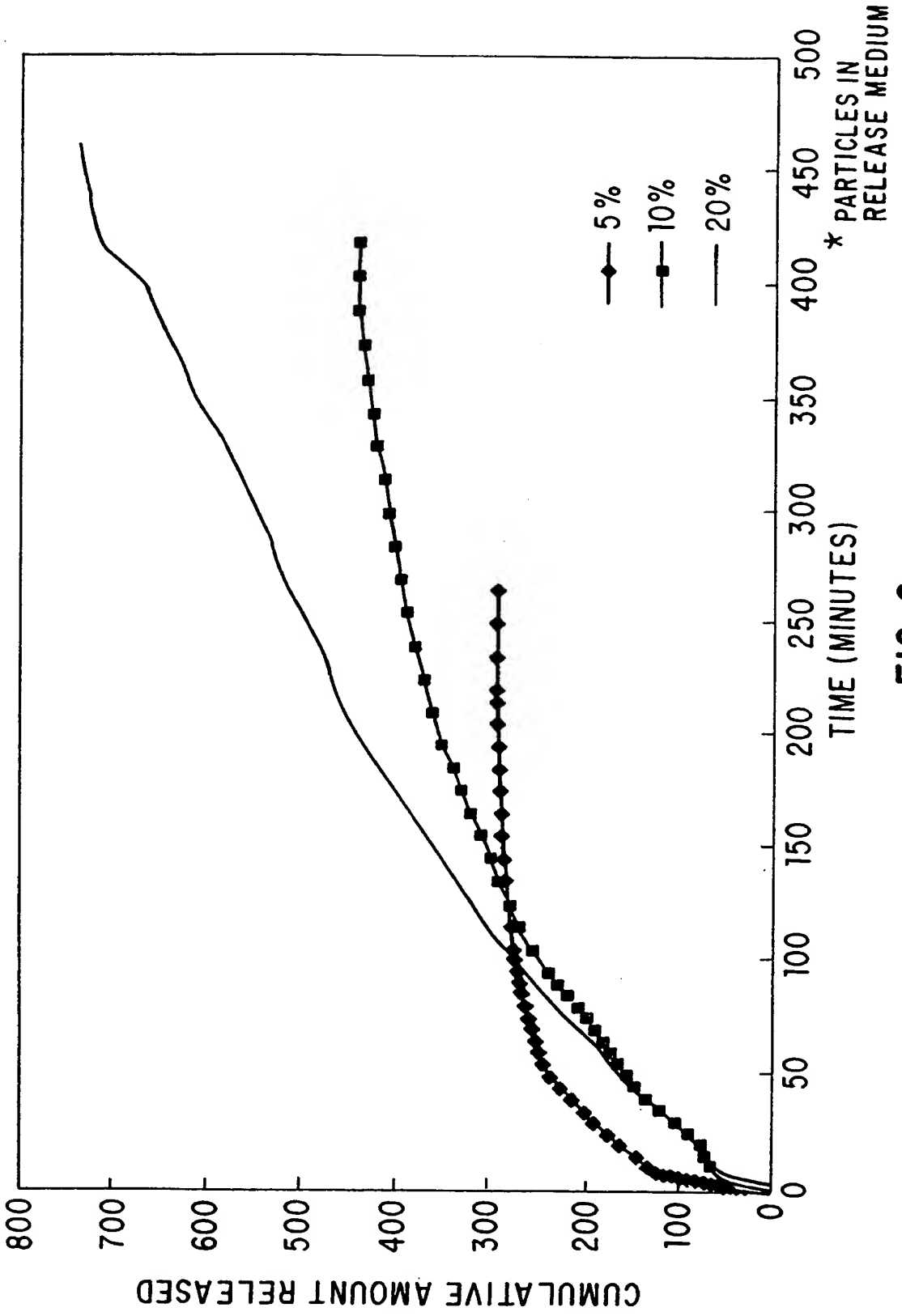

FIG. 6

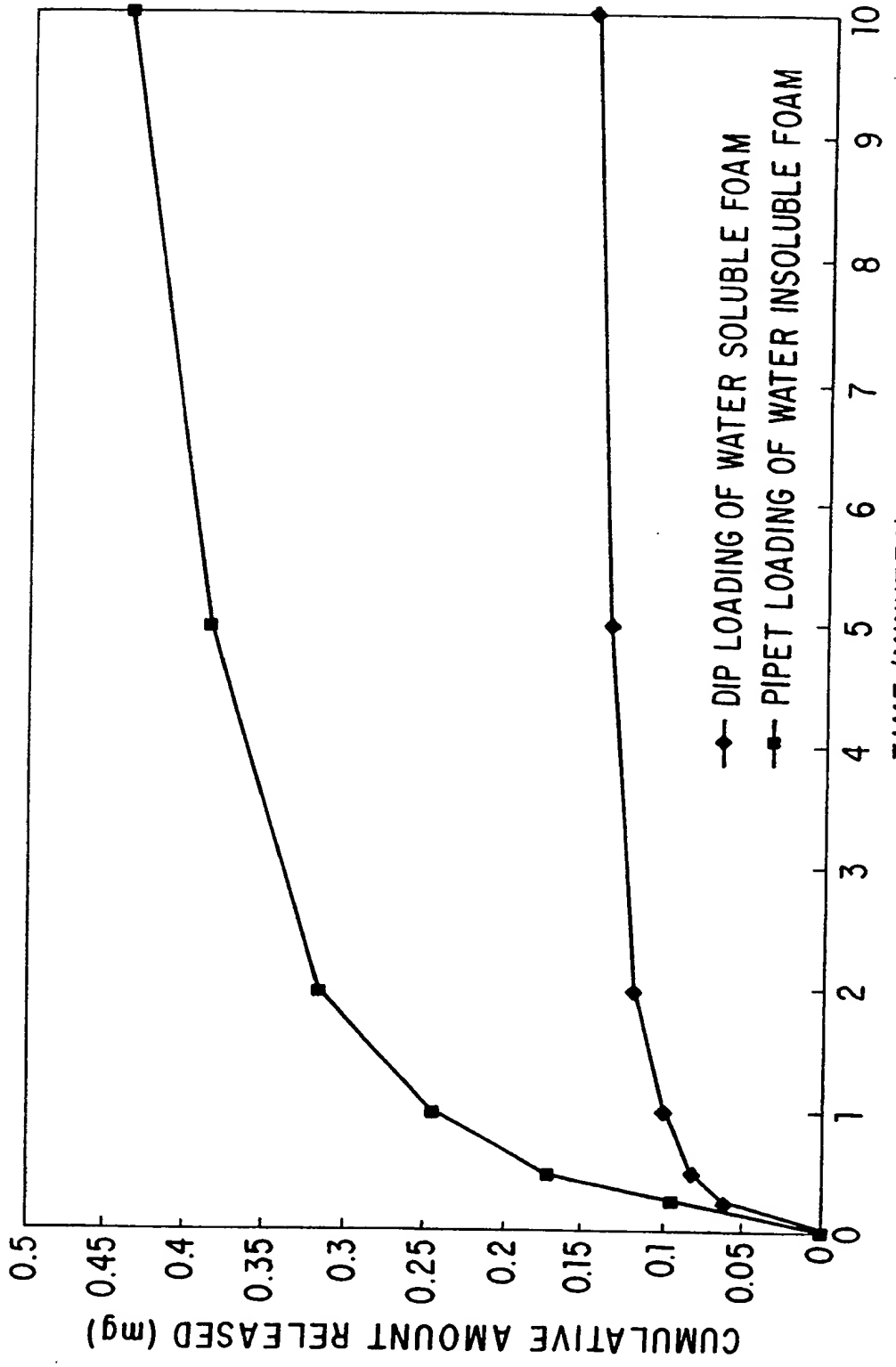

FIG. 7a

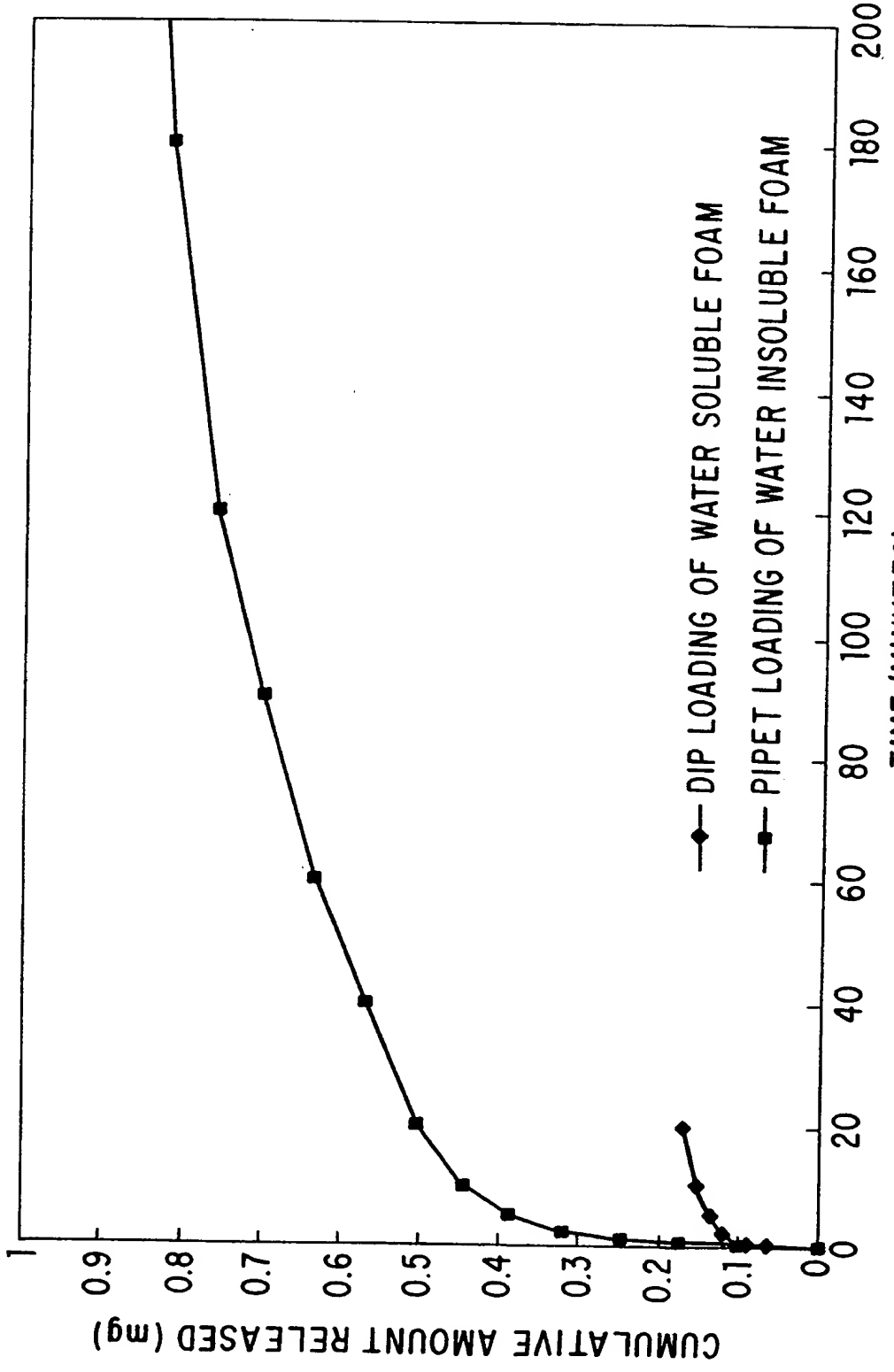

FIG. 7b

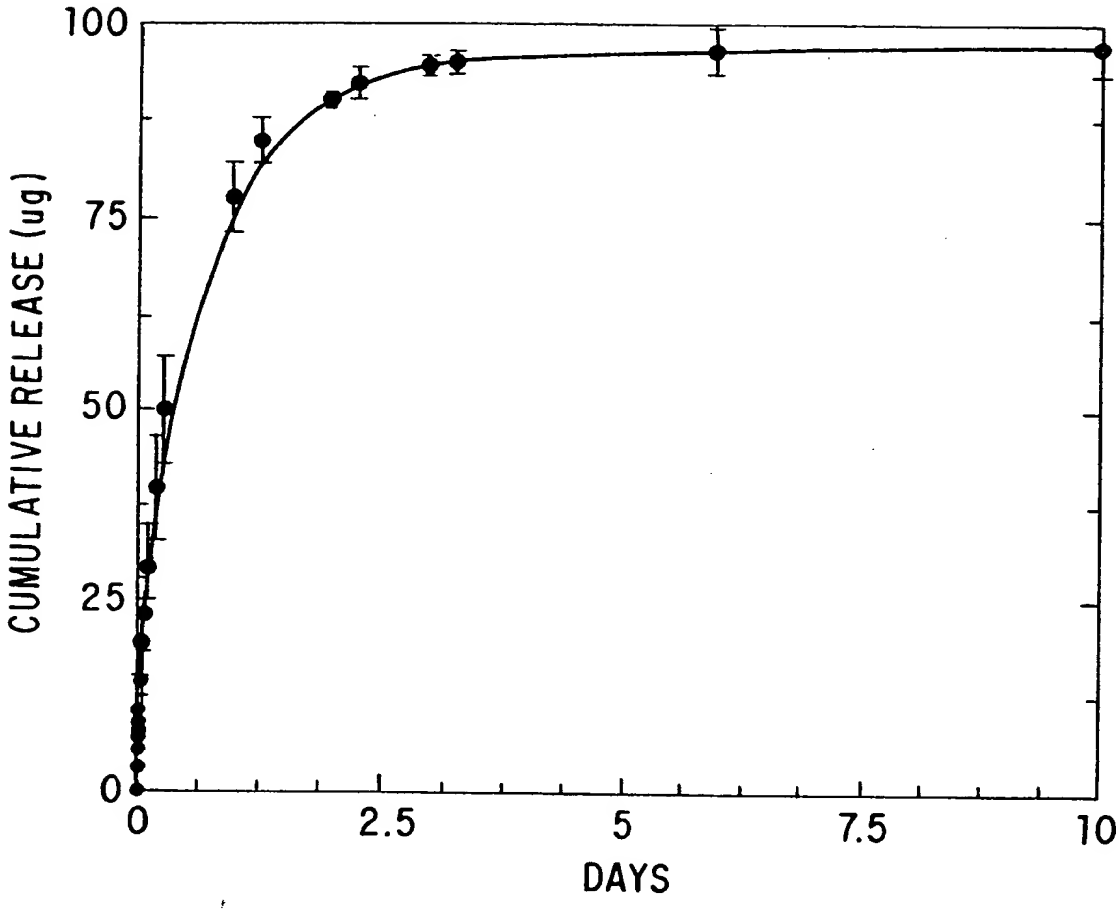

FIG. 8

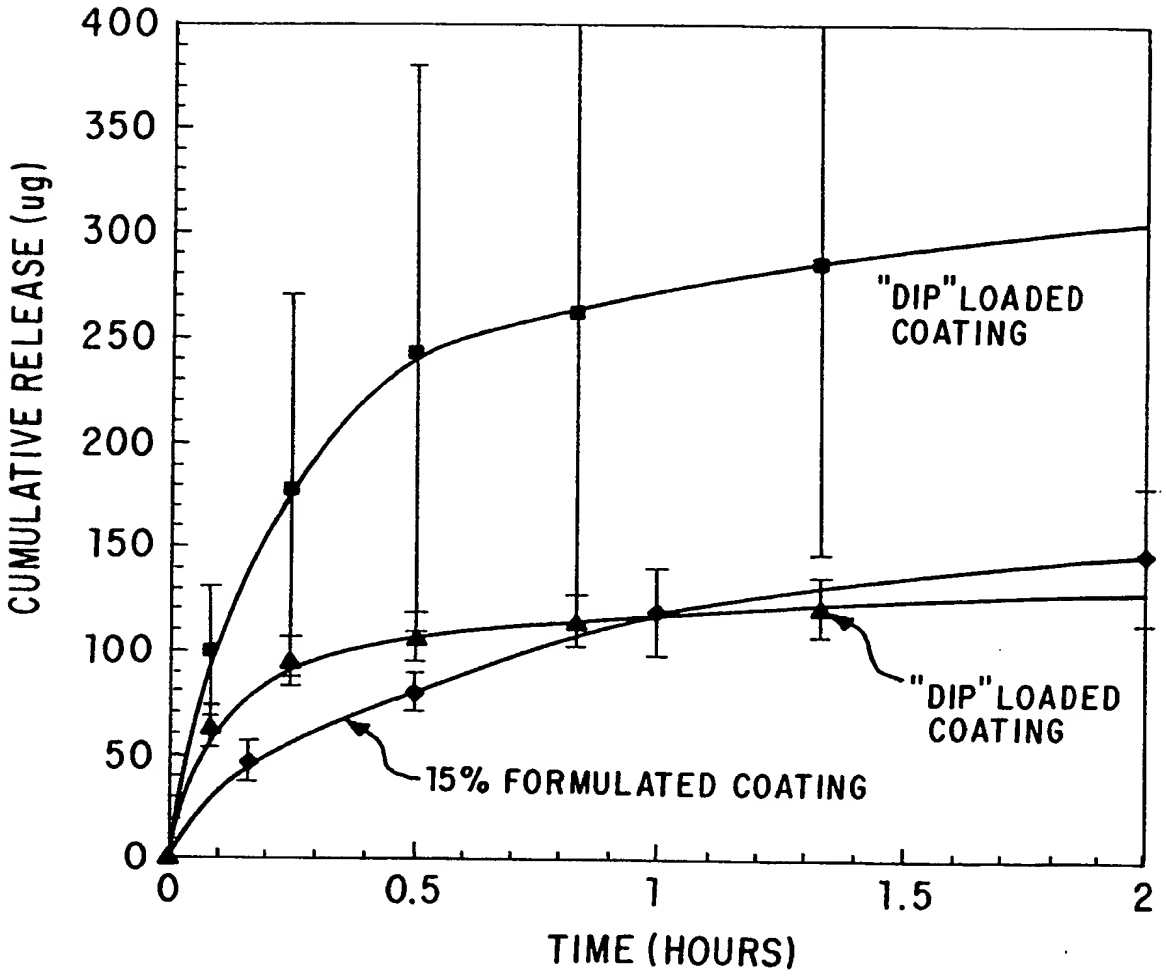

FIG. 9

INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/US 98/16775

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00 A61L29/00 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication. where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 651 986 A (BREM HENRY ET AL) 29 July 1997 see claims; examples 2-6 ---	1-43
X	WO 95 03036 A (ANGIOGENESIS TECH INC ;ARSENAULT A LARRY (CA); BURT HELEN M (CA);) 2 February 1995 see claims ---	1-43
X	WO 96 25176 A (NEORX CORP ;KUNZ LAWRENCE L (US); RENO JOHN M (US)) 22 August 1996 see claims ---	1-43
X	WO 94 21308 A (CEDARS SINAI MEDICAL CENTER) 29 September 1994 see claims; examples --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 1998	07/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ESPINOSA, M

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 92 15286 A (NOVA PHARM CORP ;SHIKANI ALAIN (US)) 17 September 1992 see claims	1-33
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X	WO 95 08305 A (JACKSON RICHARD R) 30 March 1995 see claims	1-30
X	WO 92 11896 A (BOSTON SCIENT CORP) 23 July 1992 see the whole document	1-30
X	US 5 439 446 A (BARRY JAMES) 8 August 1995 see the whole document	1-30
X	WO 93 06792 A (SCIMED LIFE SYSTEMS INC) 15 April 1993 see claims	1-30
X	WO 95 21636 A (LEPETIT SPA ;ROMANO GABRIELLA (IT); GOLDSTEIN BETH P (US); WILLIAM) 17 August 1995 see claims	1-30

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3NSDOCID: <WO___9908729A1_IA>

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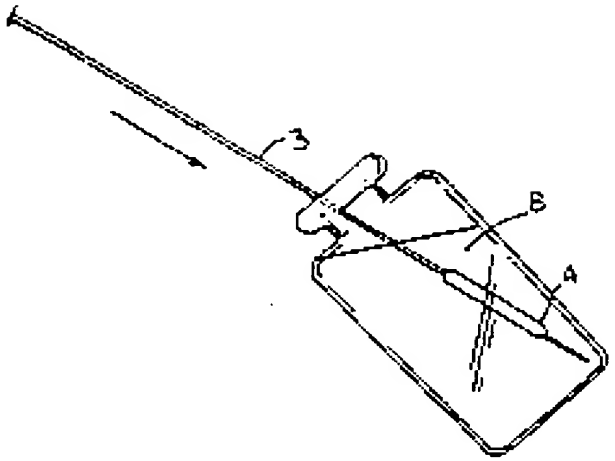

FIG. 1a

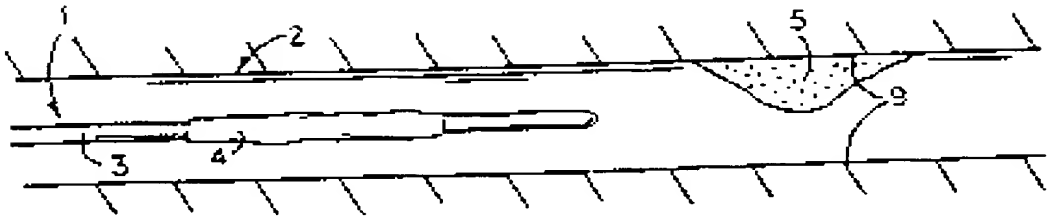

FIG. 1b

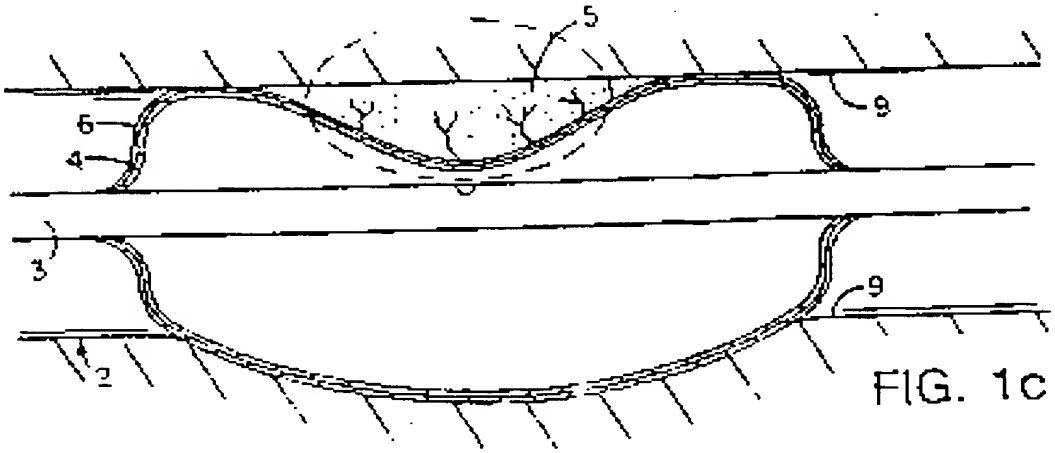

FIG. 1c

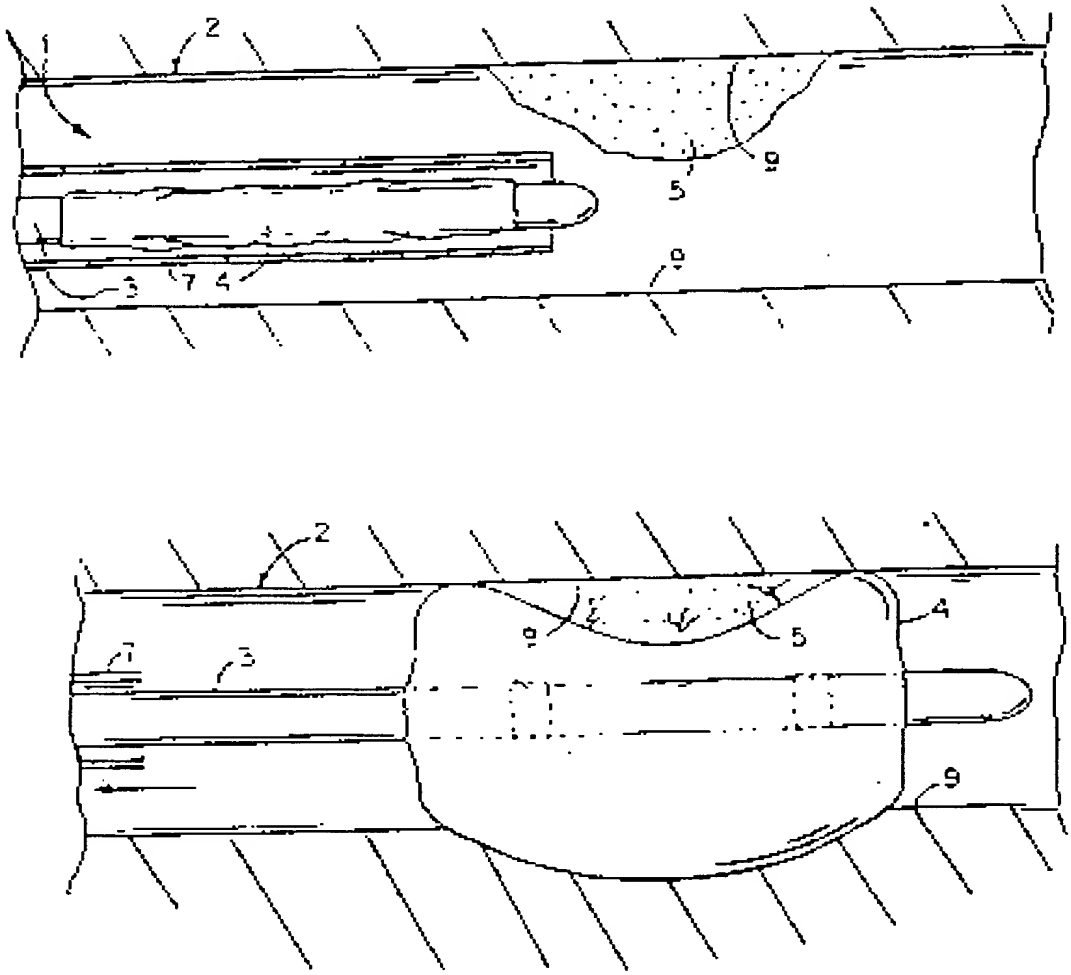

FIG. 2

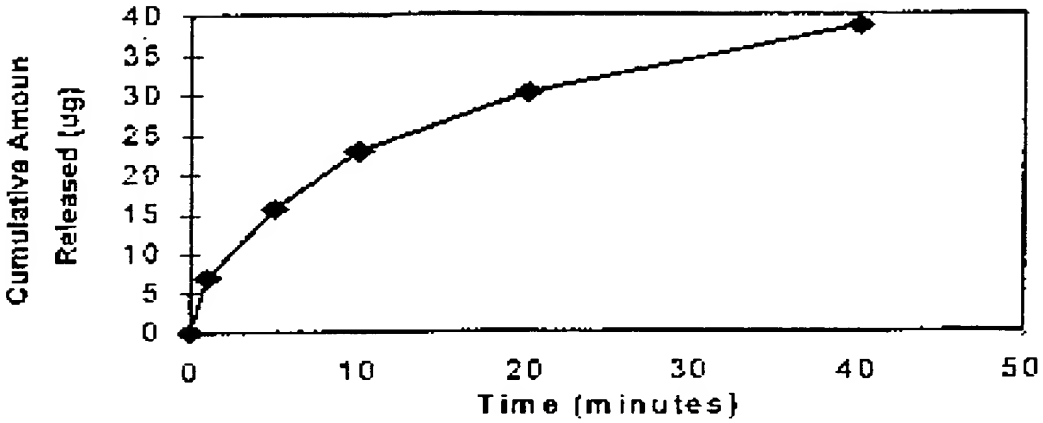

FIG. 3a

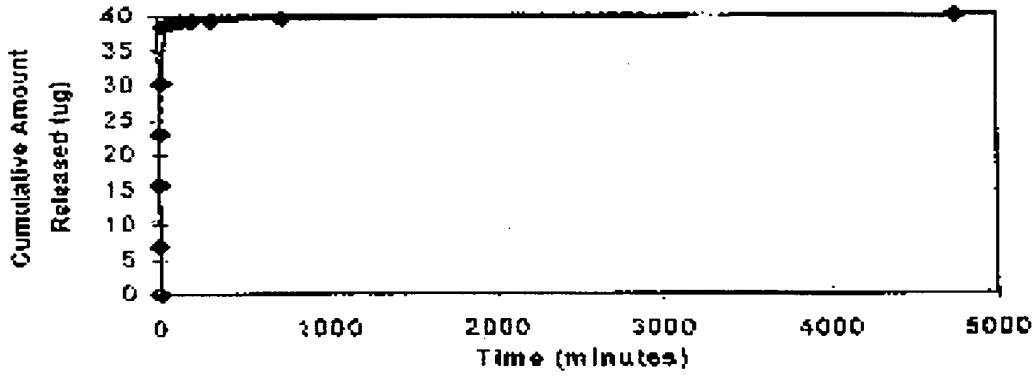

FIG. 3b

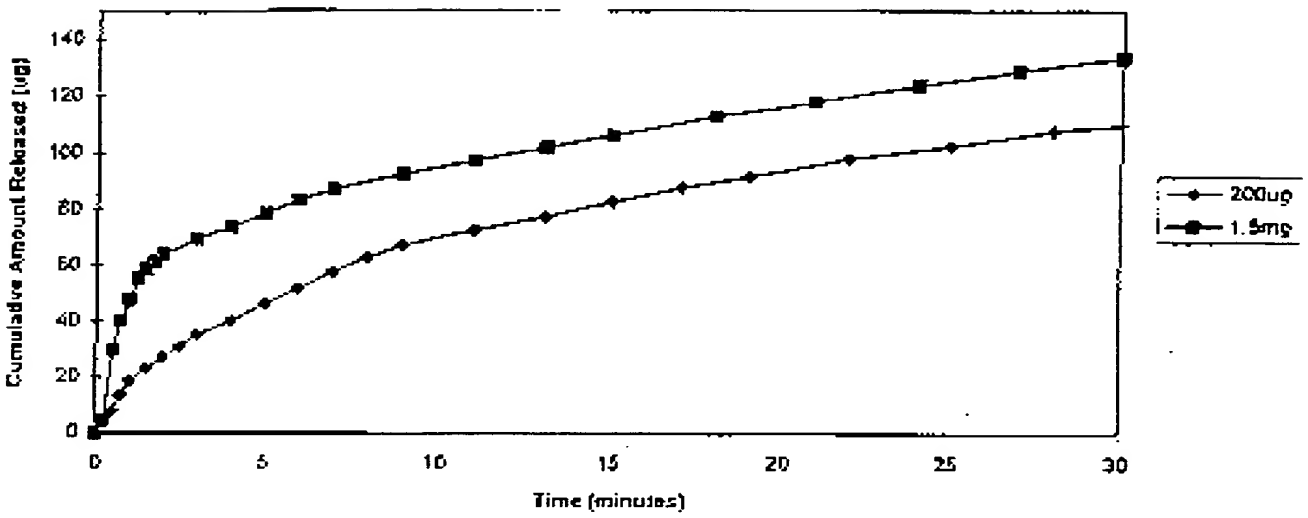

FIG. 4a

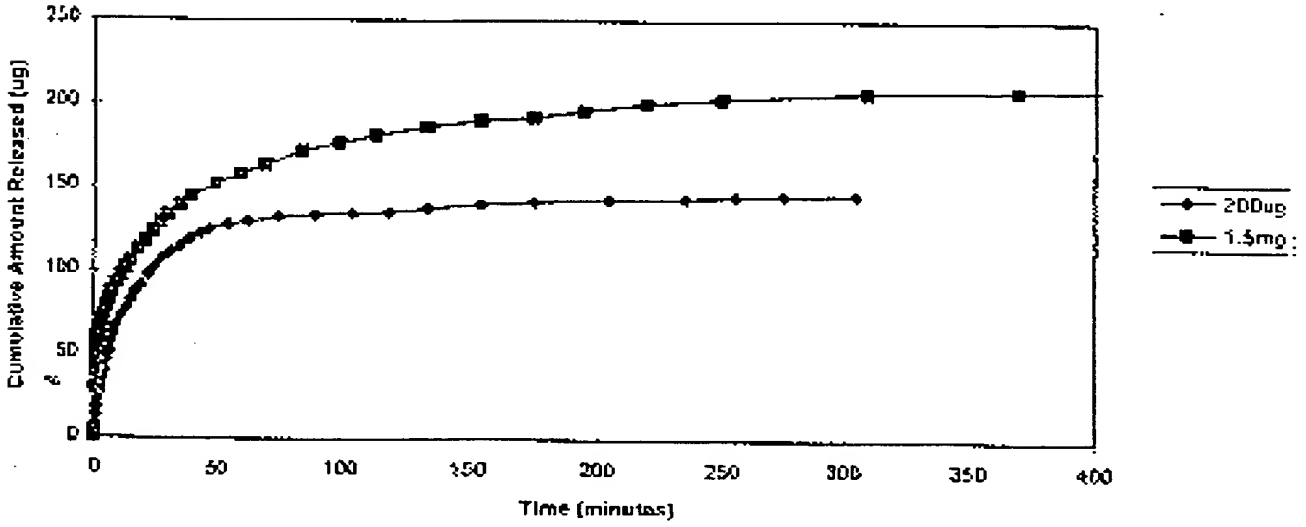

FIG. 4b

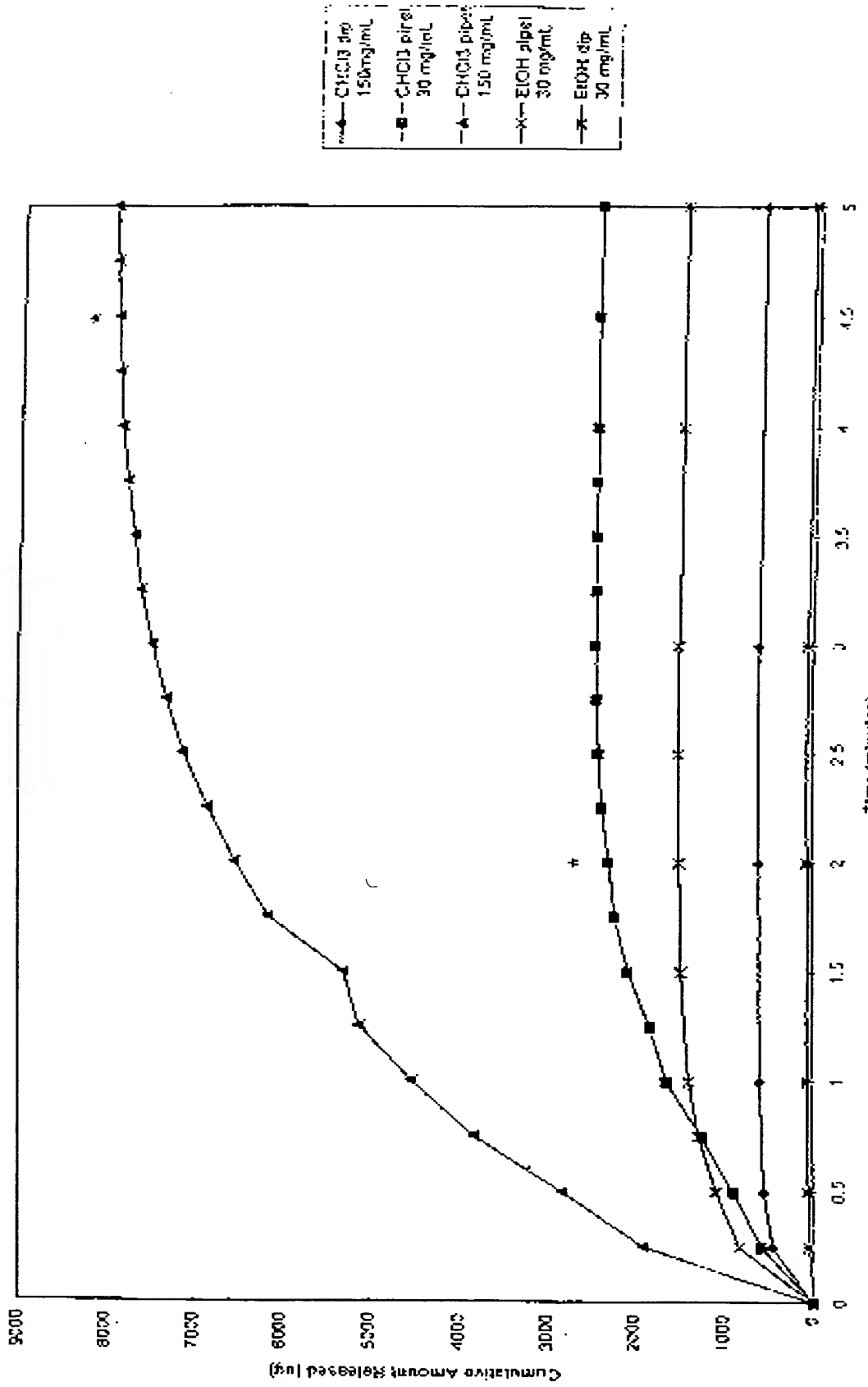

FIG. 5

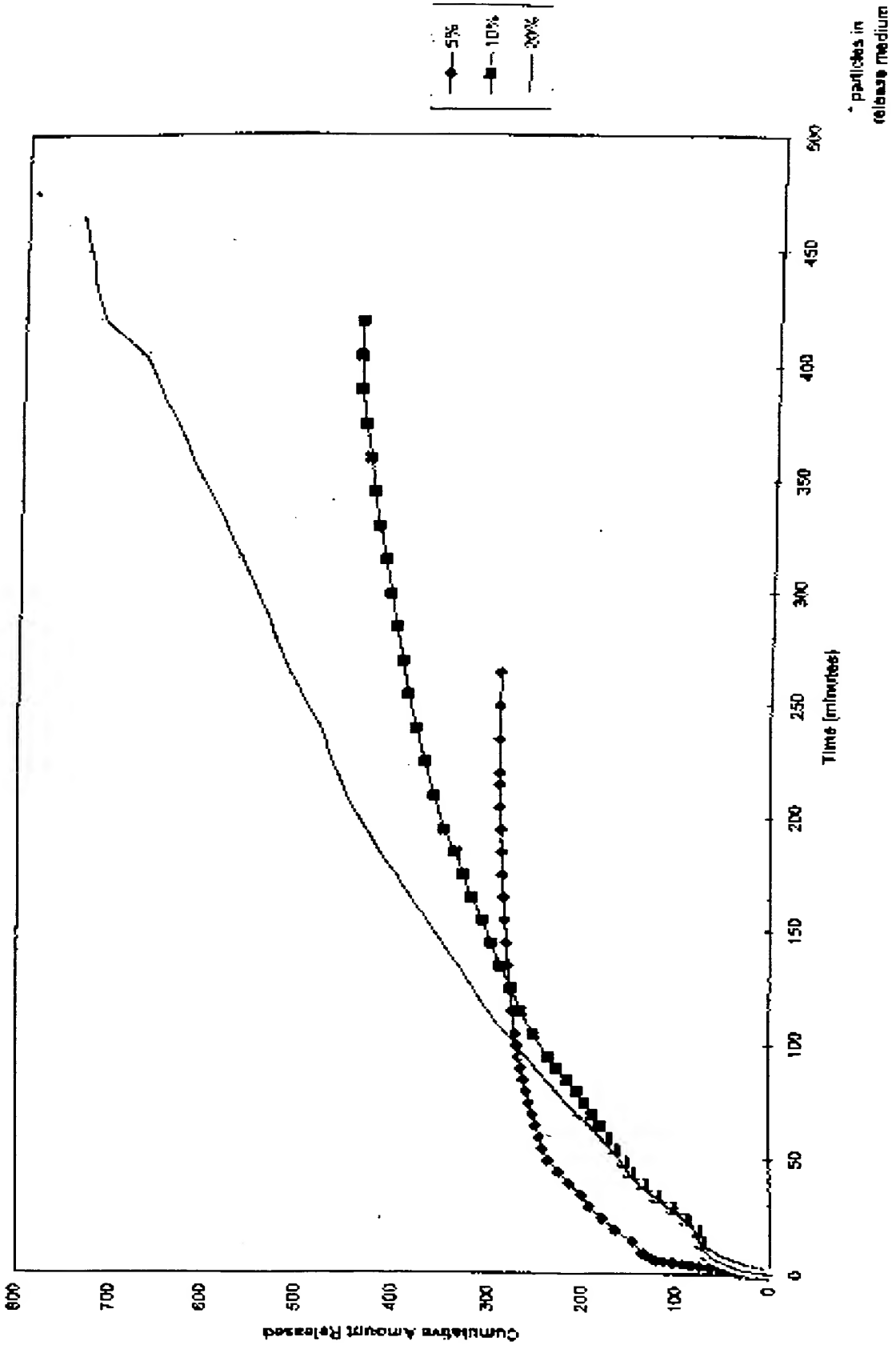

FIG. 6

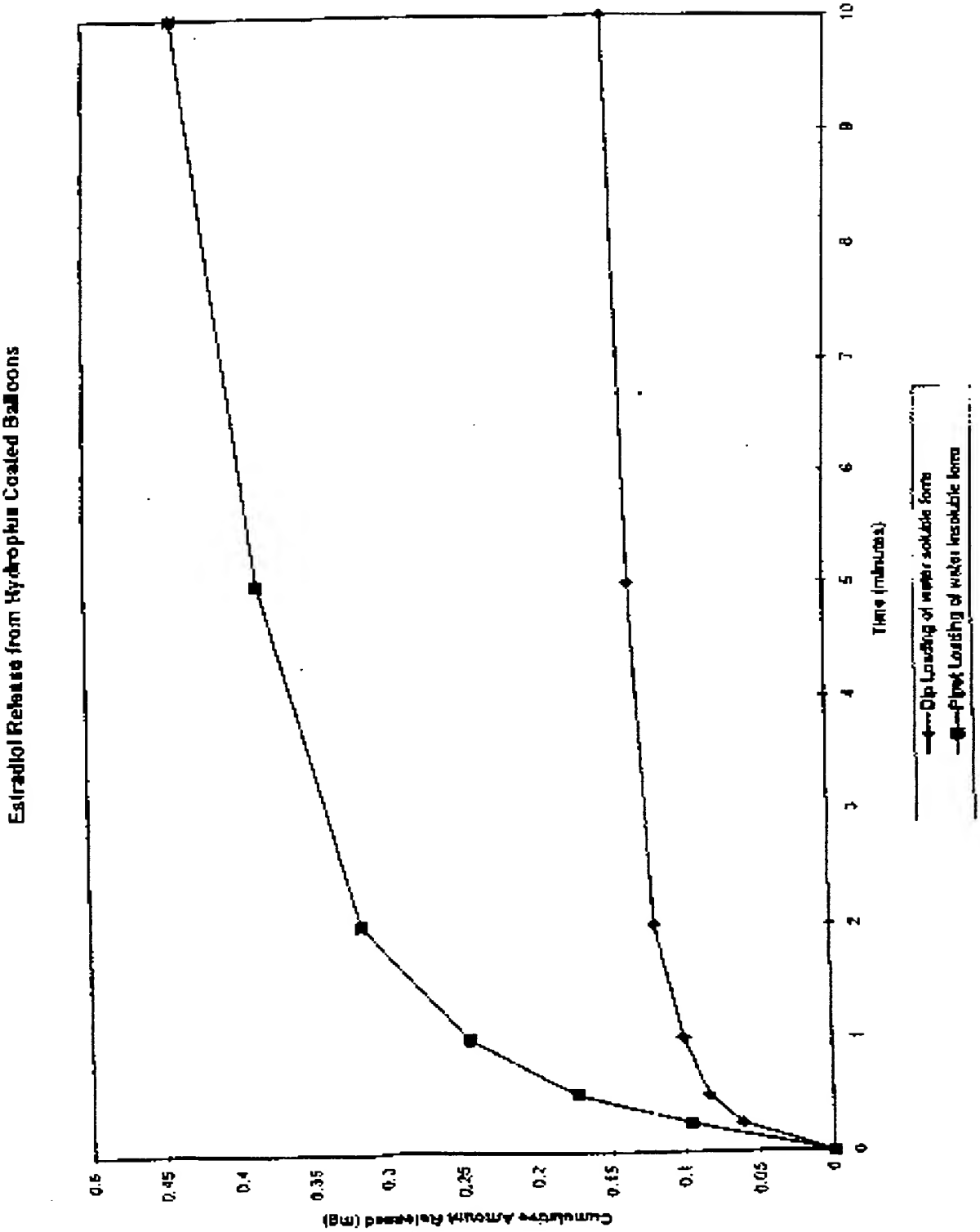

FIG. 7a

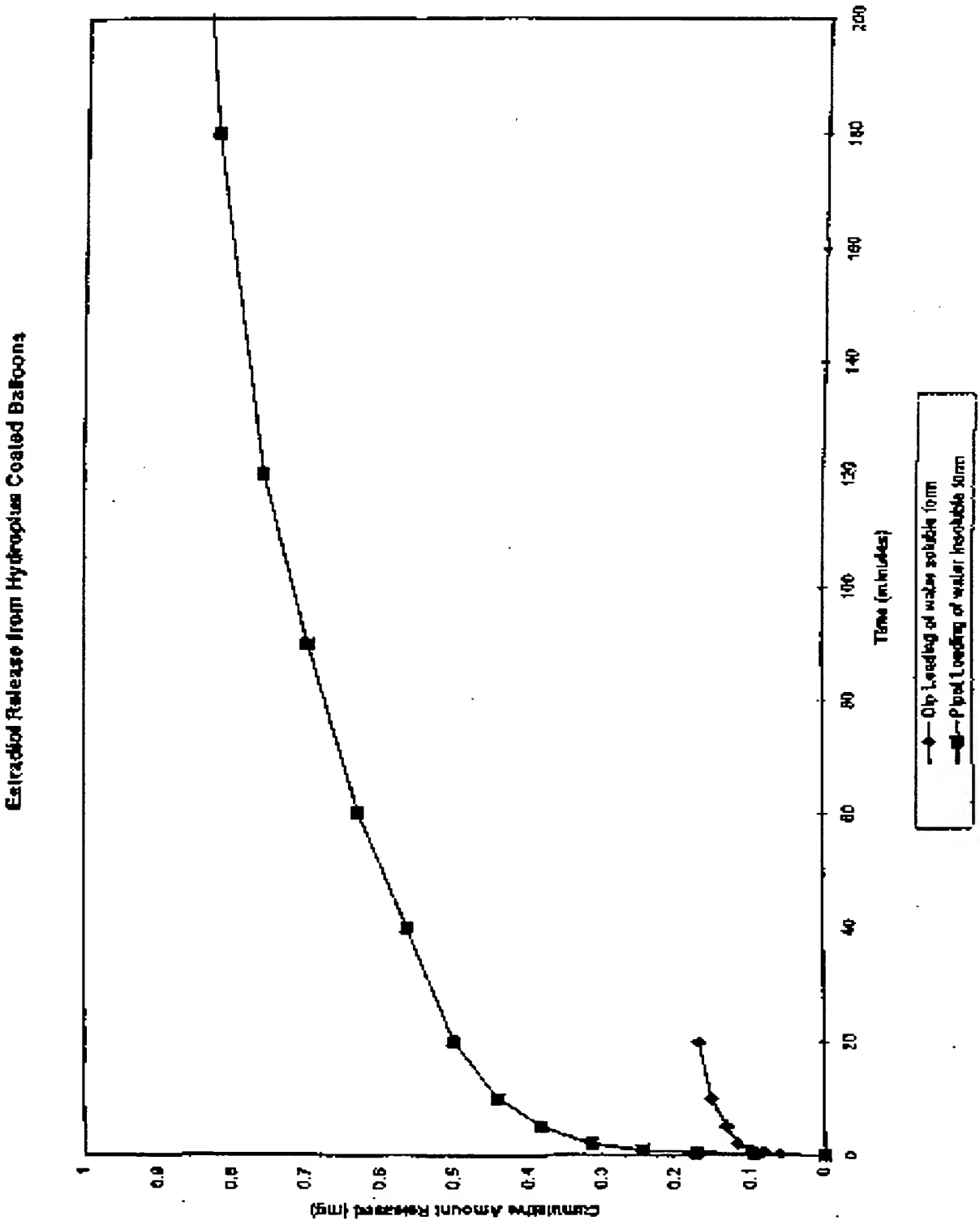

FIG. 7b

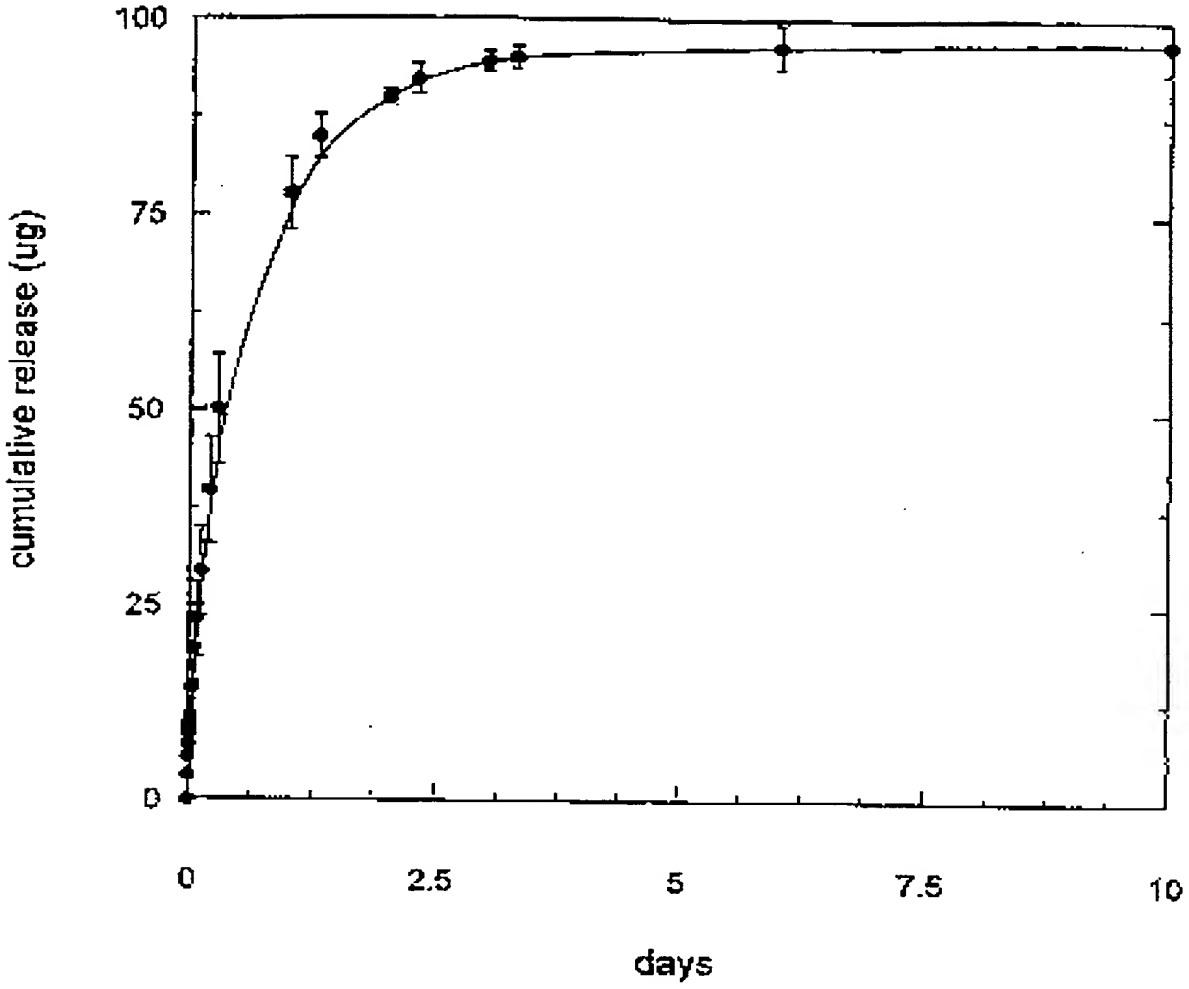

FIG. 8

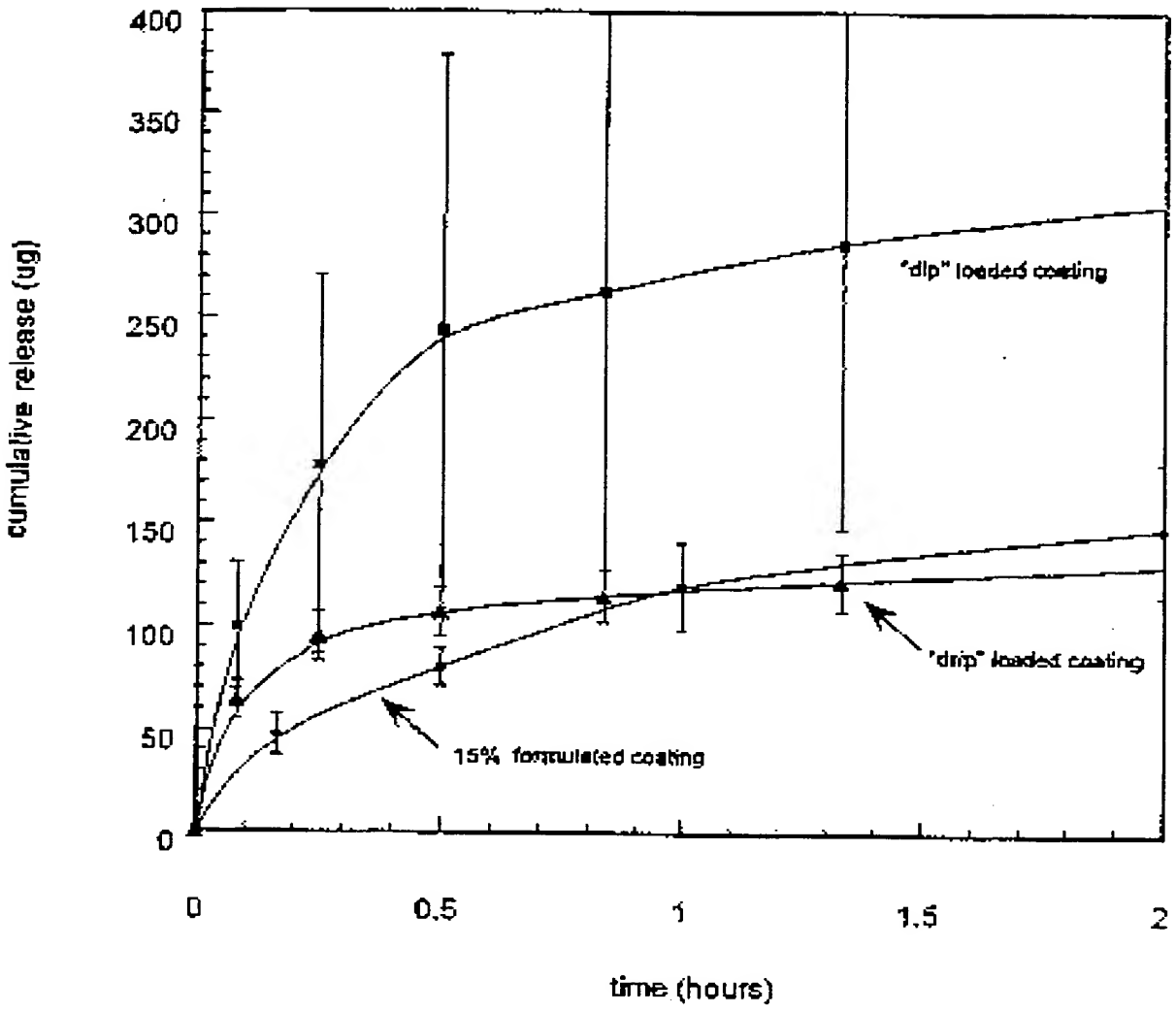

FIG. 9